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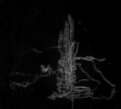

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Editorial

Clinical Electrocardiography: Offspring of Science or Empiricism?

NEARLY all clinical electrocardiographers now employ the 12-lead electrocardiogram as standard or at least basic procedure. The 9 leads designated "unipolar" are regarded as superior to "bipolar" leads, save for Einthoven's limb leads, which are credited with special values revealed by his equilateral triangle hypothesis. But if the present conformity in technic reflects widespread satisfaction with things as they are, the results of newer investigations of theory and recent studies of the consequences of ischemia in certain parts of the heart, as well as older matters sometimes swept under the rug, invite inquiry into the present state of affairs.

The assumption that patterns of potential fluctuation transmitted to an electrode in contact with the heart, can be recorded without serious degradation in electrocardiograms, provided the other electrode is placed away from that organ, although contested in the past, has long been widely accepted. But when electrode positions are limited to the body surface, the possible approaches toward such an objective appear to be (1) finding a reference position where potential fluctuations are relatively small and (2) the use of devices to achieve partial or complete cancellation of potentials from 2 or more positions. The acceptance of centric dipole hypothesis, even to the limited extent of accounting for the distal body surface potentials, should move one toward the second approach. This is the approach of the Wilson procedure, which by deriving its theoretical basis mainly from Einthoven's historic hypothesis attempts a complete or practically complete cancellation as implied by the term "unipolar lead."

Einthoven and Wilson conformed to scientific procedure when they stated the assumptions, mostly untested, upon which they based their hypotheses. The fact that this state of affairs imparted a provisional status to unipolar lead theory, appears to have escaped mention by most writers on clinical electrocardiography. V-lead values can be derived from lead systems in which an electrode attached to the right arm, left arm, or left leg is substituted for the central terminal in precordial leads, provided the values of leads I and II are known and time relations are taken into account. Thus because the basic data of the 12-lead electrocardiogram are found in 8 other leads, it is repetitious to a degree and claims for its superiority must rest upon the arrangement of differences of potentials in what is regarded as a unipolar form. Exploration of the body surface using V leads has reflected what appears to be a complex state of affairs so far as the distribution of ventricular potential is concerned and has provided recommendations for numerous leads to supplement the 12-lead electrocardiogram. The phenomenon of "decrement" or preservation of patterns of differences of potential varying in minor degree save for amplitude of deflections is observed over limited areas only, unless limb leads are of small amplitude. Such findings are in striking contrast with those obtained when the reference electrode is placed over the right upper part of the back, by which large areas where decrement exists can be demonstrated with corresponding reduction in variety of ventricular patterns and simplification of relationships.[1] Finally the uniform distribution in V leads of the "unexplained deflection" of right bundle-branch block over an area that

includes the right side of the precordium and the right arm, in contrast with decrement in the other deflections of the QRS complex, has not been reconciled with unipolar lead theory.[2]

Irrespective of these phenomena, unipolar lead theory requires examination at the level of its essential assumptions. With respect to the important assumption of homogeneous conduction, various attempts have been made to measure the resistivity of living tissues in situ. To what extent the technical difficulties of such measurements have been solved, remains to be decided by those competent in this pitfall-laden field. A conclusion upon that point is a necessary preliminary to evaluation of error in unipolar theory introduced by this assumption, not only in the light of well known differences in blood versus tissue resistivities but because of their structural relationships, especially in the heart and lungs. In the past, questions regarding dipole eccentricity as a possible objection to Einthoven's hypothesis were usually dismissed as quibbles. Nevertheless, theoretical analysis by Frank and studies in models by Frank and Kay (in experiments that accept the conditions of a finite dipole and homogeneous conduction) have shown that central terminal technic should exhibit an important deviation from unipolarity in human beings because of dipole eccentricity.[3] Thus, one of the essential theoretical supports, not only for unipolar lead technic, but also for certain long-cherished notions regarding limb leads, has become dislocated. If this is all that is seriously wrong with unipolar lead theory, the possibility of salvage exists. In fact, if by appropriate corrections phenomena now almost quantitatively predictable from limb leads, such as the unexplained deflection and the uniform S-T segment displacement sometimes recorded in all precordial leads, could be eliminated, the unipolar thesis would be relieved from the burden of accounting for an influence of limb leads upon precordial leads.

Sufficient time has not yet elapsed for careful examination of the new cancellation technics designed to demonstrate the existence of "mirror" (actually inverse) patterns of potential. One may venture to predict that not all will surrender promptly to the implication of finality suggested by this work. Already the comparably good cancellations obtained by different methods based upon somewhat different theoretical concepts appear to require explanation.

What can be said regarding the various vectorcardiographic procedures recently proposed? For one thing, the basic assumptions are too divergent for all these procedures to be equally firmly grounded, and without new evidence we shall not know whether any is. There seems little reason for objection to the proposal of a vectorcardiographic or electrocardiographic procedure for clinical use without reference to theory, if one is prepared to defend his procedure upon practical grounds such as the correlation of findings with subsequent adequate pathologic data. Indeed until theory is further advanced, there seems no alternative course by which any technic proposed for clinical use can be justified.

We cannot at present dispose of the question raised in the title regarding the relative contributions of science and empiricism, and, one might add, incompletely validated hypothesis to clinical electrocardiography where only results count. But whenever better methods can be developed than those sanctioned by particular notions concerning theory, so much the worse for such notions. For there seems little doubt that when sound theory is established there will be little difficulty in recognizing the best methods.

CHARLES C. WOLFERTH

REFERENCES

[1] WOLFERTH, C. C., LIVEZEY, M. M., AND WOOD, F. C.: Distribution of the patterns of ventricular potential which determine the forms and significance of electrocardiograms. Am. J. M. Sc. **205:** 469, 1943.

[2] — AND —: A study of methods of making so-called unipolar electrocardiograms. Am. Heart J. **27:** 764, 1944.

[3] FRANK, E., AND KAY, C. F.: Frontal plane studies of homogeneous torso models. Circulation **9:** 724, 1954.

The American Heart Association—Its Aims and Accomplishments

Presidential Address

By Edgar V. Allen, M.D.

FOR several years I have had the opportunity to work closely within the structure of committees of the American Heart Association. It has been my great pleasure to become acquainted with many people—scientists, physicians, business men and women, and other people—interested in man's welfare. Moreover, I have been privileged to observe the fine work carried on incessantly by members of the full-time staff in the Central Office of the American Heart Association. Again, in the past few months, first as President-elect and then as President of the American Heart Association, it has been my good fortune to come to know volunteer workers in many parts of the country, as well as members of the staffs of affiliates and chapters.

This experience has been most gratifying but also singularly enlightening to me. I have come to understand how impressively the quality of the people interested in the Heart program, as well as their great interest and sustained efforts, have made it possible for the American Heart Association to progress so magnificently to a well co-ordinated, effective attack on the various problems of diseases of the heart and blood vessels. "Incurable diseases are only those the doctors don't know how to cure."

It is not too much to say that, working together, we have swept away some of the darkness of the unknown in our part of the civilized world and have come a long way toward revelation of the solution to some of man's oldest ills. We know enough now to be able to say that we have added far more to the sum of knowledge of human infirmities than our forebears ever thought possible.

What I wish to do here is not only to thank those who have contributed so much, but also to tell the story of the American Heart Association—a story that surely is drama in our times.

At the beginning, 9 years ago, when the American Heart Association first became a national voluntary health agency, many ideas were extant that might be likened to a helter-skelter of building stones. The resultant confusion can only be imagined. Then, by means of countless committee meetings and sustained interest, the tumbled building stones were slowly put into place to form a sound, pleasing, and efficient edifice: the American Heart Association. Fortunately for us, many ideas relating to the Association are still flourishing, but, as I see them, these have to do largely with how we shall attain our goal, rather than to how we shall define that goal.

Like the fabled Flying Dutchman, I have been up and down the land as the chief representative of the American Heart Association. I have of course visited with many people, and everywhere I have noted, in addition to willingness to contribute to the attainment of our goals, considerable vagueness as to the program of the American Heart Association. My task here therefore resolves itself into dissipating, so far as I am able, any semblance of doubt or obscurity about the program of this remarkable organization. Let us begin with research and what we conceive it to be.

The Meaning of Research

Research is a persistent struggle to find the truth. "Research is an organized method for keeping you reasonably dissatisfied with what you have." Medical research seeks to disclose the hidden meaning of life, of health, of disease, and of death. If man had emerged from the dark and distant past into the bright industrial and economic present without the salubrious heritage of research in the field of disease, he probably would have emerged ridden by more diseases and infirmities than he

could possibly conquer, and it might well have been that they would have vanquished him and his progeny.

As a result of research, countless beneficial substances and procedures are available to us now: penicillin and other antibiotics; insulin for the treatment of diabetes; effective means of preventing acute inflammatory rheumatism; the use of anticoagulants, improved methods of treating high-blood pressure; surgical operations on the heart and blood vessels which give promise of even happier achievements to come; vaccination and immunization. Yet these are only a few of the accomplishments of research. Most of them have come to us only after years of onerous toil and very often hours of seeming frustration.

Yet, if research had not been done, millions who now are healthy adults would have died in infancy; many, many mothers would have died in childbirth, and the average expectancy of life in this country would have been nearer 39 years, as it was a hundred years ago, rather than 70 years, as it is today.

Research is conducted in all fields of medicine and in various surroundings: in the laboratory, at the bedside and in the operating room. Research requires scientific training; the quality of persistence in the face of discouragement; a desire to battle against the unknown; willingness to work without respite, and great impatience with the half-true and the obscure. Research is no profitless enterprise; sometimes it is measured in terms of resources, of tools, of men, and of public support which can be mustered in our times. But most of all, however, its gains must be measured by results. As is true of most human endeavor, the quality of research can be good, bad, or indifferent; but it is certainly true that where there is no research, there is no progress. No one knows when, from a corner of some laboratory, there will come a basic discovery which, like a brilliant beam of light, will dispel the darkness of ignorance. "It is not what we know that is so important, it is what we do not know." It is a long way from an idea to success, and the journey does not lead through lassitude and indifference.

The American Heart Association has embarked on a program of research because 800,000 Americans die each year of diseases of the heart and blood vessels, and perhaps 10 millions are afflicted with such diseases. In 1956–1957 the American Heart Association will spend about 6 million dollars for research. That seems a vast sum, but it represents only about a sixth of the expense to American taxpayers for the removal of paper and other rubbish from along the highways. Six million dollars represents a per-capita investment in health of only a trifle more than 3 cents. This observation must be viewed in an economy in which 45 million families earn more than $4,000 annually. The 6 million dollars would buy only 2,000 automobiles. The total of $20,000,000 spent by the American Heart Association and its affiliates in the 8 years of our existence represents about two thirds of the amount spent by Americans to feed their parakeets each year. Currently, the total amount spent for industrial research is 5 billion dollars annually. The total annual expenditure for medical research appears to be in the neighborhood of a quarter of a billion dollars; twenty dollars for creature comforts; one dollar for health. The program of medical research represents rebellion against physical deterioration, but the rebellion is still so small that it seems to be hardly more than an insurrection. More scientific minds, more buildings and more equipment are urgently needed.

Almost everyone has had some sorrowful experience with disease of the heart or blood vessels, or both. Almost everyone we know—a member of his family, a close personal friend, a neighbor or an associate—almost certainly will have or does have heart trouble, or he suffers from the effects of a stroke, of failure of the kidneys to work properly or of poor circulation to the legs.

When we consider such all-pervasive facts, we see clearly that there is actually no need to defend a nation-wide, cohesive, planned attack on diseases of the heart and blood vessels. Rather, we perceive that every reason impels us to extend the attack with vigor. I hope that everyone who gives money to the cause will

consider the donation to be an investment, rather than a gift. People in the prime of life are dying in great numbers from diseases of the heart and blood vessels. To prevent these deaths and to give relief to the ill is to protect oneself and one's family. Certainly, this cannot be called a charitable enterprise. Anyone who knows that disease of the heart and blood vessels kills more people less than 65 years of age than do the next 5 causes of death combined cannot doubt that his investment in research will, with the investments of others, go far toward extending either his life span or that of his progeny.

Research, then, has an intimate, significant meaning for almost everyone. It is closer to all of us than most of us realize. This much being true, how shall we organize research?

The Organization of Research

First of all, we cannot fully understand the methodology of research if we do not know how it is to be organized or how it is to be done. "A research laboratory is not simply a building that contains apparatus for conducting experiments; I contend that it is a state of mind." For that reason, some attempt at explanation may be useful to you, as it has been instructive to me.

In the beginning, then, must be the definition. The paramount need of the Association is for the inquisitive mind, the explorative mind, the mind that never can be content with the established order of knowledge, but is incessantly seeking to add to it. "Just the minute you get satisfied with what you've got, the concrete has begun to set in your head."

The possessor of such a mind we regard highly in the parent organization of the American Heart Association, so highly, in fact, that we encourage him to choose what he wishes to investigate. We try to make it possible for him to go where he can do his work best. We free him, as much as possible, from administrative distractions. We allow him plenty of time in which to prosecute his studies. Finally, we provide him with an income which is sufficient to allow him to do his work in the way I have sketched it. Incidentally, about 56 per cent of funds received by the National Office of the American Heart Association are spent in support of research.

Categories are useful to all of us. They help us to keep our fingers on the essentials and they exclude the trivial. We have set up simple categories in the research field at the national level to help in understanding the work that is done in investigation and to show the status of those who do it.*

Career Investigatorship. A Career Investigator, under our unique definition, is a mature scientist who is assured of lifetime support for his investigations at an income comparing favorably with that of a full professorship. We have 3 Career Investigators now. More will be added. They are accorded the benefits of added funds for equipment, material, and laboratory workers. We think the category of Career Investigatorship is almost without parallel in the realm of scientific awards.

Established Investigators. We have 79 workers in this category. They are skilled, competent scientists fully qualified to carry out their inquiries independently, and they have a tenure of 5 years to encourage them to do so. If their work gives evidence of promise, the tenure may be extended for a second 5-year term. In some respects this category is comparable to a proving ground, for especially gifted workers may be chosen from it to become Career Investigators.

Research Fellowships. We now have 73 men who are Research Fellows. They are younger men, not yet highly skilled in methods of investigation, who work under the supervision of others who are highly skilled in their fields. The tenure of a Research Fellow is 1 or 2 years. The category actually is one of considerable opportunity and boundless advancement, for it is from this group that the experienced investigators of the future will emerge.

These 3 categories are indispensable, we think, to the stimulation of younger men, so

* The following statements about research apply only to the parent organization of the American Heart Association. The affiliates and chapters, which retain 75 per cent of funds collected in their geographic areas, have additional research programs.

that they will be attracted to scientific investigations in fields that hold the attention of this Association.

Grants-in-Aid. Still another category having to do with research is the grant-in-aid. This year 186 such grants have been made. In effect, such a grant sustains the cost of research by placing technical assistance and supplies in the hands of experienced investigators.

This is a good program, but not good enough. There are additional areas of research that need continuing consideration, such as greater support of research by affiliates, the allocation of uncommitted grants to individuals or institutions, the designation of specific programs followed by recruitment of qualified personnel, evaluation of programs of education and community service, better teaching of the biologic sciences in the secondary schools, undergraduate student education, and the recruitment of more and better minds for research. In addition, we need to consider, on a continuing basis, financial support for construction of research facilities. Although the growth of the American Heart Association has been great, it should continue at an accelerated pace; the help and interest of a greater number of volunteers are desirable, even though about a million solicitors were on the job on Heart Sunday. Finally, there must be unremitting study of needs for staff personnel, both as to quality and to quantity. Everyone wants staff work to be done well; conversely, there is need for avoidance of "over-staffing" and of expenditure of too high a portion of income for administrative purposes. We must avoid becoming so intent on our inner development that we lose our sense of accountability to the society that supports us. I know that in the regional meetings of staffs this year, ways were found to refresh the springs of research and make them flow in increased quantity. "Research is the science of making changes in a scientific way." In addition, the factor of research must not fail to be of continuous concern to committees of all heart associations.

Effects of the Research Program

It is still too early for appraisal of the ultimate results of the scientific research program. I am convinced, however, that the program is sound, and I am persuaded that it is bringing into existence a body of trained workers who will be imbued with the inexorable determination to push back the frontiers of the unknown that now limit so much of what we know about the diseases under study. This research program gives us what we never had before: a corps of especially gifted investigators who will devote a large portion of their lives to the study of specific problems without any cause for interruption of their labors or deviation from their objectives. It is reasonable to suppose that in the course of their work these research scientists will train others, so that we may expect a cycle that will never come to dead center. Every accession of knowledge gained thereby is a form of compensation for the great generosity of those who have supplied the funds that we expend. The dissemination of what is learned, the impetus to new research, the application of the results of investigation, and the constant increase in the ranks of skilled and dedicated investigators surely are rewards that should point inevitably toward the ultimate conquest of disease. "Intelligent ignorance is the first requirement in research."

I have been asked, on a number of occasions: "Do you expect to keep people alive forever?" The answer of course is, "No—not forever." Nevertheless, with minor exceptions, people want to live. The desire to live is as old as man. Who can say what a normal life span should be? Is it 70 years, 80 years, 90 years, or 100 years? It is eminently wise that further attempts should be made to prolong life and to maintain health. If such attempts had not been the aspirations of a hundred years ago, our life expectancy today might well be 39 years instead of 70 years.

The Problem of Disease

I have spoken somewhat about the philosophy of the American Heart Association, the organization of its research projects, what I think the effects of its research program can be, and something of the financial aspects of the work of the program under way by the Central Organization. We ought now to give

some attention to the diseases that currently are the major concern of the Association. In the main, they are 3, and the 3 of them cause at least 90 per cent of the deaths that can be attributed to diseases of the heart and blood vessels. These are rheumatic heart disease, high-blood pressure, and hardening of the arteries. Another problem still incompletely defined has to do with coagulation of the blood. There is the matter of impairment of coagulation of the blood indefinitely and by simple means. There is also need for study of means of dissolving blood clots within arteries and veins. The trinity of stubborn diseases, which I have mentioned, and the formation and dissolution of blood clots point up the need for continuing aggressive research, for although we can define disease processes and can explain the effects they produce, we still do not know what is the essential cause of them. "People think that if they have a name for a thing they understand it." New and probably very basic knowledge about causes is what we lack at present, and well-conceived and intelligently executed investigation is the only way to get such information.

I cannot say, and certainly no one would be foolhardy enough to claim, that for a given amount of funds we can produce cures for the several diseases against which we are striving. The scientist usually proceeds from a foundation of basic facts that are known. We do not have these basic facts, so far as causation is concerned. Hence, in research on cardiovascular disease the paramount emphasis inevitably must be placed upon the acquisition of knowledge about basic causes. This in turn requires the exercise of much patience and resolution. At the same time, there is no reason why methods of treatment should not improve, as they certainly have improved, while we are still occupied in the search for basic causes. We cannot expect immediate answers to the multitudes of questions before us, but we ought not to fall into the grievous error of assuming that no progress is being made simply because the basic causes of these diseases continue to elude us.

Actually, we all know that some people today are living useful and relatively normal lives who 15 or 20 years ago would have died at an early age or would have subsisted as invalids. Treatment has advanced most remarkably. Dr. Paul D. White has said that more progress in the conquest of cardiovascular disease has been made in the past 20 years than in the preceding 2,000 years. We can thank the physicians and scientists for this splendid achievement. I am pleased that this is so. Yet we have to face the fact that 800,000 Americans continue to die annually of disease of the heart and blood vessels. This is a sobering reflection when we find ourselves in an expansive frame of mind about modern progress in the attack upon these particular diseases.

Death and disability are never governed by geography. What research discovers in New York City can be put to the benefit of the people of Idaho, Maine, Oregon, or of almost any other part of the world. All over the world there are people, and as people we are all susceptible to the assaults of the same antagonist in the form of diseases of the heart and blood vessels.

Secondarily, may I suggest that affiliates, working with their boards of directors, should endeavor to devote a higher proportion of their organization's income to research either in their respective geographic areas or through the Research Allocations Committee of the American Heart Association. I have mentioned this point before, but I am convinced it is worth additional emphasis. It is largely through the rewards of research that all of us, as well as our children, can benefit from, as well as justify, the mighty flood of dollars that has come to us from the boundless generosity of the people of America.

The Program of Education

The American Heart Association carries on an active program of education. For physicians there are our official publications, *Circulation*, *Circulation Research*, and *Modern Concepts of Cardiovascular Diseases*. The last goes to about 100,000 physicians and medical students. We have an annual national scientific program that attracts the attention and the participation of the finest minds in the nation in both treatment and research. Then, there are

numerous meetings sponsored by affiliates. There are numerous other programs for specialists in the field of diseases of the heart and blood vessels, for general practitioners and physicians generally.

The philosophy behind all this professional education is quite simple. People can receive the best possible care only if physicians are fully informed. The ultimate goal of research is not mere acquisition of knowledge, but, rather, the widest possible dissemination of that knowledge and the application of it to the care of patients.

The American Heart Association carries on an active program of education for those of our citizens who are not scientists or physicians. In the year 1955–1956 many millions of pieces of literature were mailed from the central office of the American Heart Association; much of this vast quantity of literature was for the purpose of lay education. In addition, there have been multiple but uncounted radio and television programs. I believe it to be true that the American public has been and is being superbly educated in the matter of diseases of the heart and blood vessels. Yet we are not satisfied—an even more active program is being planned. "The price of progress is trouble."

The Community Service Program

I have said that the ultimate goal of research is not only the acquisition of knowledge but also its widest possible dissemination and application to the care of patients. While the primary link between the laboratory and the patient is the individual physician, there are often situations in which the fullest application of knowledge requires resources greater than any individual patient or physician can provide.

Prevention of disease—for example, prevention of recurrences of rheumatic fever—is one of the areas in which the resources of the many must often be brought together to supplement and enhance the efforts of the individual physician, always, naturally, with his support and help. Rehabilitation—the need to provide work and a return to usefulness for those of our citizens afflicted with diseases of the heart and blood vessels—is another such area. These are two of the main fields in which we feel the development of community services can help ensure that widest application of knowledge which is the objective of research.

In every talk I have given, I have supported the idea of community service and education, and I have strongly advocated such an idea in private views. I have also said that research is our major effort. Now I would place these two statements in their proper focus, so far as the Heart Association's program is concerned. Research is the wellspring; professional and public education and community service are the channels through which we help lead the lifegiving stream of knowledge to the people who are to benefit from it.

In developing community programs that meet the particular needs of their own people, Heart Associations must of course work with other health groups, both to ensure their own greater effectiveness and to avoid duplication of effort. For example, through the National Heart Institute, the United States Public Health Service is also active in the field of community service. It follows that our program of community service must be coordinated with that of the National Heart Institute as well as with others, lest we spend money injudiciously—money so freely given to the American Heart Association and its affiliates. Such coordination is being actively pursued at the national level.

In line with this concept of avoiding duplication, one of the most useful programs developed by many local Heart Associations has been the information and referral services through which heart patients seeking help can be directed to facilities or agencies already provided by the community. Often, as a result of their familiarity with existing resources, Heart Associations learn of some pressing need which is not being met and which no other agency in the community is in a position to meet. This need may be the lack of a valuable diagnostic instrument at the local hospital or clinic, for example, or the lack of personnel to follow up children for whom prophylactic drugs have been prescribed to ward off recurrences of rheumatic fever. In such cases the full value of the physician's skill or recommen-

dations is not being realized. Under circumstances like these, Heart Associations may find a way to meet the need. Naturally, they should always assess the need for the particular community service in terms of their entire program.

What I have said about community services should not blur the importance of the individual's own responsibility to act for himself, as far as possible. At this point I would recall to you the inherent honesty and wisdom expressed in the credo of Abilities, Incorporated, resolutely and even defiantly written by a group of people who ordinarily would be considered to be disabled. These are the words:

> I do not choose to be a common man. It is my right to be uncommon if I can. I seek opportunity, not security. I do not wish to be a kept citizen, humbled and dulled by having the state look after me. I want to take the calculated risk, to dream and to build, to fail and to succeed. I refuse to barter incentive for a dole. I prefer the challenges of life to the guaranteed existence, the thrill of fulfillment to the stale calm of Utopia. I will not trade freedom for beneficence, nor dignity for a handout. I will never cower before any master nor bend to any threat. It is my heritage to stand erect, proud and unafraid, to think and act for myself, enjoy the benefit of my creation, and to face the world boldly and say, "This, I have done."

New and Challenging Problems

I should like now to consider some entirely new problems currently before the American Heart Association.

Student Education. I may say at the beginning what many of us already know: that we have a deficit of trained scientific minds and, to a lesser degree, of physicians interested in diseases of the heart and blood vessels. With this deficit in mind, the American Heart Association is establishing a division of Student Education. Plans have been made for active cooperation of this division with the Student American Medical Association. As one means of creating maximal interest on the part of students, I suggest that affiliates develop in their respective medical schools a thesis contest; the author of the best essay, as selected by the faculty of the school, would receive a modest financial reward, but one sufficiently attractive to ensure participation in the contest. This is a desirable endeavor because it offers an opportunity for justifiable publicity at the time of the presentation of an appropriate citation and a special medal to the winner of the award. Moreover, the expenses of the winner of the award for travel to the annual Scientific Assembly of the national association would be paid by the affiliate or by the recipient of the cash award. In addition, some physician or scientist would be appointed to guide the winner about the assembly, so that he would not be lost amidst the hectic activities of the annual session. He would be privileged to attend the scientific sessions, the meetings of the assembly, and the deliberations of the various panels. The message he would take back to his fellow medical students could not have other than a lasting and favorable impression on them.

Encouraging the Interest of High-School Students. The American Heart Association plans progressive stimulation of interest of high-school students in careers in medicine and biologic research. "A research problem is not solved by apparatus; it is solved in a man's head." One of the media which we hope to use is television, and the television programs will be provided at a time when there is the greatest viewing audience of high-school students. The use of television obviously is enormously expensive, and it cannot be supported by Heart Funds while we continue to carry on and extend our present program. Hence, for this special but extremely important activity we need a sponsor or sponsors. I have conducted correspondence with a number of presidents of corporations about this matter. In addition, the subject has been discussed at the meeting of the National Radio and Television Committee, which was attended by many representatives of the radio and television networks and advertising agencies. Mr. Rome Betts, Mr. Fred Arkus, and I had an appointment with Mr. Edward Stanley, director of the public-service programs of the National Broadcasting Company, on February 20, for discussions on this vital aspect of our work.

I am sure that there are many who will have some ideas in this respect that will help us, and I hope they will transmit them to me.

You may not know that we have to compete with industry, which carries on an extensive and active program of recruitment in secondary schools, colleges, and universities. Even the Federal Bureau of Investigation has an active program for the recruitment of young graduates. It is obvious, I believe, that the attraction of good minds into industry, for example, can result only in a steady decrease in the numbers of capable young people who will be interested in careers in the biologic sciences, and current reports from responsible medical and scientific educators indicate that this unfortunate decrease has already begun.

We must work actively to maintain and improve our own position in this matter of assuring a reservoir of competent medical and scientific research manpower. The matter is being considered actively on a national level by the Committee to Review Research Policy. At the last annual meeting of the assembly of the American Heart Association, the panels on "Five-year Planning" and on "Research" recommended that the American Heart Association and its affiliates consider the recruitment of research manpower at the high-school and college levels, and support such recruitment efforts as may yield results. It was further recommended that support of teaching of the subjects of diseases of the heart and blood vessels in medical schools be considered on a limited and personal basis. These recommendations have been approved by the Board of Directors of the American Heart Association. In addition, Dr. Irvine H. Page, past president of the American Heart Association, has recommended that active attempts be made to improve the quality of teaching of the biologic sciences in the secondary schools. "Research is an organized method of finding out what you are going to do when you can't keep on doing what you are doing now." Such a program will require much thought and consideration to ensure that it is conducted with the utmost possibilities for success.

The affiliates and chapters of the American Heart Association should send into our high schools capable speakers whose specific purpose would be to attract the interest of high-school students to careers in medicine and the biologic sciences. I have found that high-school students are discerning, and that they are not much impressed by "big names." Hence, speakers should be selected on the basis of their ability to present their material in an impressive and interesting manner, rather than upon their position in the community.

Recently, General Mark Clark, Dr. Page, and I had a conference with the President of the United States about some of the matters that I have presented. I am hopeful that substantial and tangible results will come from that conference.

Reprise

I continue to be amazed that so many Americans contribute so much and so wholeheartedly to the American Heart Association. I often ask myself, "Why?" Very likely no simple reply would be forthcoming. Among the reasons must surely be considerations of the very highest altruism, such as the sense of quiet fulfillment, which arises from the selfless devotion of the generous to those who are unfortunate, disabled, and infirm.

Immanuel Kant, in a famous pronouncement, which has since attracted the speculations of philosophers and moralists everywhere, said that every man should conduct himself according to maxims which he would be willing to have translated into universal law. For our own purposes, this could mean that in meeting and transcending the natural frailties of the human will and spirit, we could depart at last from life secure in the conviction that we left it better than we found it.

Such a conviction surely must be among the foremost of the reasons why so many thousands of our citizens incessantly and unsparingly give their devotion and support to the American Heart Association. The mass of men who are about to leave this existence probably do not have much regard for what happens to it after they have left it, but there still remain multitudes who do. The works they have done were carried out without the spur of ambition or the thought of recompense, and it is in such a spirit and in such a concept that I wish to remember the great numbers of resolute citizens who have provided us with the means

of whatever advances we have been able to make against the stubborn and formidable adversaries of man's health and well-being.

As President of the American Heart Association I am imbued with a sense of profound humility, for whatever I am able to do and whatever success I may attain will depend preponderantly upon the help and the labors of others. Great enterprises are never instituted, brought to consummation and perpetuated by the efforts of one man, and the vast objectives of the American Heart Association never could be realized without the collective generosity, determined resolution, and untiring labors of thousands throughout the nation who are accorded no especial distinction and seek none.

In closing, I should like very much to leave with you a fine old truism of which I do not know the author: "For never hath any man attained to such perfection but that time or use hath brought addition to his knowledge, or made correction, or admonished him that he was ignorant of much that he thought he knew."

The homely wisdom of that sentence should do much to confer the priceless gift of humility upon any man, whatever his stature in the affairs of men.

For all of us, whatever the station we hold, there are the vibrant words of one who herself knew hopeless infirmity and physical misery for most of her life, Elizabeth Barrett Browning: "The sick man thou hast served will make thee strong: the poor man thou hast served will make thee rich."

Finally, let me say again that, despite the giant strides we have taken against the disease killers of men, our toilsome journey has only just begun. Our path lies over a hundred difficult and uncharted hills into the future. And here it is, too, that we shall need the persistence, resolution, stamina, and labor of all of us, for we all can remember how, in John Bunyan's homely but powerful annals of a simple man's progress upward, Christian fell into the Slough of Despond and rescued himself, almost before his journey was begun. I cannot doubt that what lies at the end of our own pathway will be, as Christian found it, bright, resplendent, and in weighty measure a contribution to the salvation of man.

Note. The short aphorisms subjoined in quotation marks in this text are known as "Ketteringisms," and are the products of the gifted American scientist and research worker, Charles F. Kettering. They were called to my attention by Dr. William H. Feldman, of the Mayo Foundation.

Clinical and Hemodynamic Studies of Myocardial Fibrosis

By ROBERT E. NYE, JR., M.D., FRANK W. LOVEJOY, JR., M.D., AND PAUL N. YU, M.D.

In many instances myocardial fibrosis mimics constrictive pericarditis so closely, both hemodynamically and clinically, that the diagnosis can be made with certainty only at operation or autopsy. In the 3 cases presented here certain distinctions can be made that suggest that the differentiation can sometimes be made by careful analysis of pressure contours from the right heart.

EXTENSIVE replacement of myocardium by fibrous tissue produces a syndrome of intractable heart failure that clinically resembles chronic constrictive pericarditis in many ways. M-shaped complexes in the right atrial pressure pattern, and an early diastolic dip and high end-diastolic plateau in the right ventricular pattern, similar to those originally described in constrictive pericarditis,[1-4] have been found also at cardiac catheterization of patients with myocardial fibrosis.[5-7] Since surgery is helpful only in the former disease, the possibility of differentiating these 2 conditions is attractive. This paper presents clinical and hemodynamic data in 2 patients with myocardial fibrosis, and in a third patient with myocardial fibrosis made as a probable diagnosis at exploration, in an attempt to determine whether any useful differential points can be found.

METHODS

Venous cardiac catheterization was carried out in the usual way, 1 or 2 hours after a light breakfast, by introducing a no. 7 or no. 8 long, single-lumen, Cournand catheter through an antecubital vein. Intracardiac pressure was measured with a pressure transducer* and recorded on a 4-channel direct-writing oscillograph.† Mean pressures were measured by planimetric integration of records for 2 (or sometimes 1) respiratory cycle. The arbitrary zero level for all pressures was 6.5 cm. behind the angle of Louis, with the patient supine. Oxygen consumption was measured continuously in an open circuit system, with room air as the inspired gas.[8] Cardiac output was determined by the direct Fick principle. Blood oxygen and carbon dioxide contents were measured with the Van Slyke manometric apparatus.

CASE REPORTS

Case 1. S. B., a 33-year-old male engineer had been in good health until December 1953, when he developed a fever associated with a harsh systolic apical murmur and 1 conjunctival petechia and was hospitalized. There was no leukocytosis, but β hemolytic streptococci were cultured from blood. Treatment with 2.4 million units of penicillin per day was begun. During the next 2 months his fever gradually subsided, but tachycardia persisted, and a gallop rhythm appeared. The heart began to enlarge and the murmur changed in character. There was an episode of thrombophlebitis of the right leg and another suggesting infarction of the spleen. Digitalis was administered. Acute rheumatic fever was suspected but there was no response to salicylate administration, and the serum concentration of alpha-1 and alpha-2 globulin was normal.

The patient was discharged in March 1954 and re-admitted in May 1954 complaining of cough, breathlessness, nausea, vomiting, and diarrhea. There were further cardiac enlargement, intensification of the apical systolic murmur, hepatomegaly, and marked elevation of venous pressure (250 mm. saline). There were no pulmonary rales or peripheral edema. Temperature, white blood count, and erythrocyte sedimentation rate were normal. Constrictive pericarditis was suspected, and he was transferred to Strong Memorial Hospital for investigation. On admission he appeared very ill and orthopneic.

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* Statham Laboratories, Inc.

† Stanborn Poly-Viso Cardiette

Clubbing, cyanosis, and edema were absent. The cervical veins were markedly distended. The lungs were unremarkable. The heart was enlarged to the left and right, and a triple rhythm and harsh precordial systolic murmur were noted. The second pulmonic sound was accentuated and split. The blood pressure was 110/95. The liver edge was felt 10 cm. below the costal margin, and there were signs of ascites. The spleen was not palpable.

The electrocardiogram (fig. 1) revealed sinus rhythm, right axis deviation, vertical electric position, and inversion of T waves in leads 2, 3, aV_F, and V_1 to V_6. Fluoroscopically there was generalized cardiac enlargement, with moderately active pulsation of both ventricles. A teleroentgenogram of the chest is shown in figure 2.

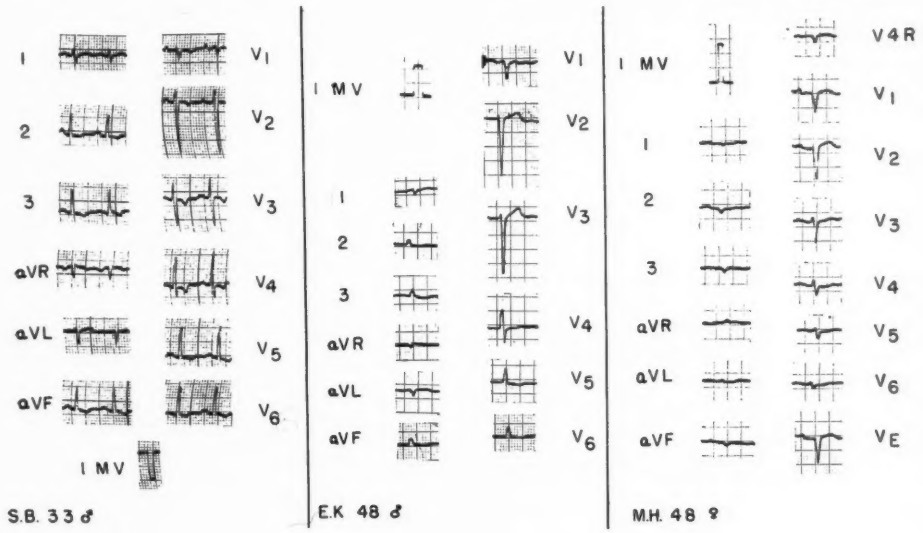
Cardiac catheterization was performed on June 4 (table 1). The principal findings were oxygen unsaturation of arterial blood, postcapillary pulmonary hypertension, marked reduction of cardiac output, and right ventricular failure. The pressure contour of the right ventricle (fig. 3) consisted of an elevated systolic peak, an early diastolic dip descending below the baseline during inspiration, and a high end-diastolic plateau approaching, or in a few tracings equaling, one third of the systolic pressure. The right atrial pressure contour (fig. 3) contained small *a* and *c* waves. The *v* wave was followed by a prominent *y* descent, followed by a rapid rise to an end-diastolic plateau, matching the ventricular contour. During inspiration the base of the *y* descent increased in depth, but there was little or no respiratory variation in mean pressure.

Exploratory thoracotomy was performed on June 8, 1954. The pericardial sac contained about 200 ml. of straw-colored fluid, but no pericardial constriction was found. The day following operation the patient suddenly became semiconscious and died 4 hours later.

Autopsy revealed healed mitral valvulitis, complicated by rupture of 1 or 2 chordae tendineae. The myocardium was largely replaced by dense scar tissue in the lower portion of the septum and over the apex, (fig. 4) and to a lesser extent elsewhere. Both ventricles were hypertrophied and dilated. The coronary arteries were widely patent. Acute pulmonary infarcts and an old splenic infarct were noted. The viscera were the seat of chronic passive congestion.

Case 2. E. K., a 48-year-old male printing-press operator, was hospitalized in December 1953 complaining of dyspnea, orthopnea, nonproductive cough, abdominal distention, ankle swelling, fatigue, night sweats, weakness, and weight loss, which had begun 18 months previously. He had been treated with digitalis and mercurial diuretics, but he had become refractory to treatment.

The principal findings on examination and investigation were as follows. There was no fever. The neck veins were distended. There were rales over the lower third of both lung fields and a right pleural effusion. The heart was enlarged and the rhythm was irregular due to frequent premature contractions. The second pulmonic sound was mildly accentuated. A grade II systolic blowing murmur was



CASE 1 CASE 2 CASE 3

FIG. 1. Electrocardiograms of 3 patients with myocardial fibrosis.

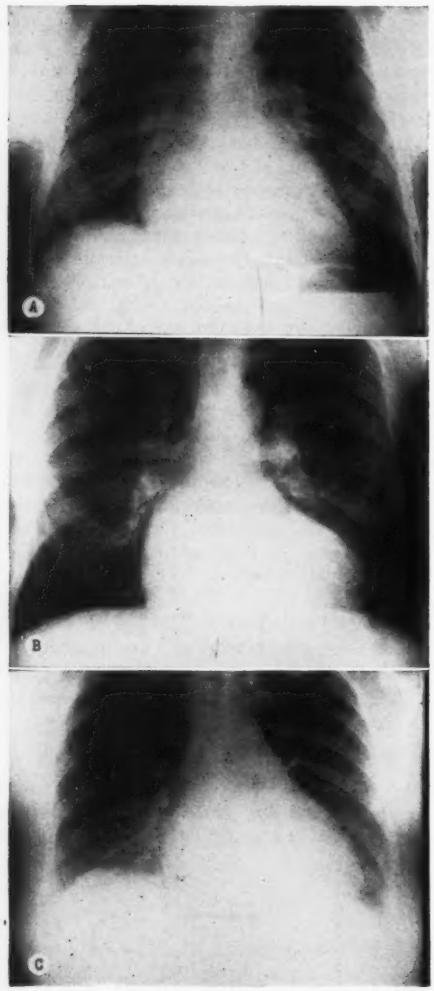


FIG. 2. Teleroentgenograms of the chest in 3 patients with myocardial fibrosis. *A*. Case 1, S. B. *B*. Case 2, E. K. *C*. Case 3, M. H.

heard between the apex and the lower left sternal border. There was ascites, the liver edge was at the level of the umbilicus, and the spleen was not palpable. There was marked edema of the legs, but no clubbing or cyanosis.

Laboratory data included a trace of albuminuria in an otherwise normal urine, a normal hemogram and erythrocyte sedimentation rate, and normal serum electrolyte concentrations. Serum cholesterol was reduced to 83 mg. per cent, (normal 150 to 200), and the icterus index was 25. These abnormalities were attributed to Laennec's cirrhosis on the basis of a history of heavy alcohol intake. The cephalin

TABLE 1.—*Myocardial Fibrosis*

	Case 1	Case 2		Case 3	
		Rest	Exercise	Rest	Exercise
Per cent arterial O_2 saturation	81	95	89	91	89
O_2 consumption, ml./M.²/min.	144	97		127	197
A-V O_2 difference, ml./L.	90	57	80	56	81
Cardiac index, L./M.²/min.	1.6	1.7		2.3	2.4
Heart rate, beats/min.	118	79		100	108
Stroke index, ml./M².beat	14	21		23	22
Pressure, mm. Hg					
Pulmonary arterial wedge, mean	22	26		27	
Pulmonary artery, mean	48	34	47	31	35
Right ventricle, S/D	51/17	60/14		44/12	
Right atrium, mean	18	10	21	12	
Resistance, dynes-sec.-cm.$^{-5}$					
Total pulmonary	1300	930		580	
Pulmonary vascular	700	240		60	
Total systemic	2600	2260		1760	

flocculation test was negative and the albumin-globulin ratio was normal.

The electrocardiogram disclosed first degree atrioventricular block and multifocal premature ventricular beats. X-ray revealed generalized cardiac enlargement, right pleural effusion, and questionable pneumonitis in the left lower lobe.

Treatment with conventional measures, including large doses of thiamine parenterally, produced some improvement and the lungs became free of rales.

During the succeeding year the patient had 3 hospital admissions for progressive symptoms of dyspnea and edema. Fever was absent except for 1 occasion, due to an associated respiratory infection. Physical findings remained virtually unchanged except that the pulmonary rales gradually disappeared. Several abdominal paracenteses and 1 thoracentesis yielded clear fluid with temporary relief. Laboratory findings were essentially unchanged. Venous pressure was 220 mm. saline. Circulation times were arm-to-lung (ether), 25 seconds and arm-to-tongue (Decholin), 32 seconds. Electrocardiograms revealed atrial flutter and then established atrial fibrillation.

By February 1955 he was severely incapacitated. Physical findings were similar to those described a year before, except that the lungs were clear.

The electrocardiogram (fig. 1) revealed atrial

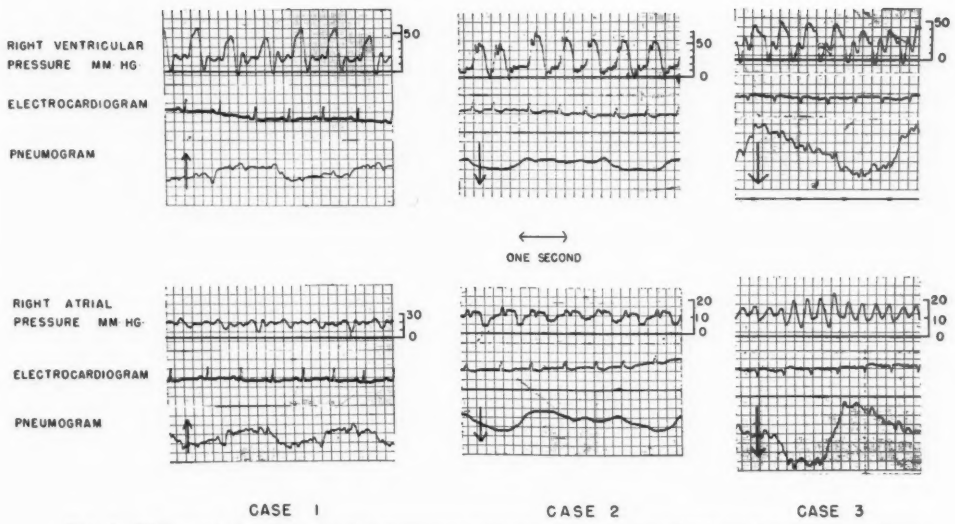


FIG. 3. Right atrial and ventricular pressure patterns at rest in 3 patients with myocardial fibrosis. The arrows on the pneumograms indicate the direction of inspiration.

fibrillation and inversion of T waves in the left precordial leads. On fluoroscopy there was a generalized cardiac enlargement with diminished pulsation. A teleroentgenogram of the chest is shown in figure 2.

Cardiac catheterization disclosed reduced cardiac output with moderate pulmonary hypertension at rest (table 1). Brief leg exercises produced marked widening of the A-V oxygen difference and accentuated the pulmonary hypertension. Arterial oxygen saturation was normal at rest but decreased during exercise. The right ventricular pressure contour, (fig. 3) consisted of an elevated systolic pressure, an early diastolic dip, which descended below the baseline during inspiration, and a gradually rising diastolic pressure. During the longer diastolic pauses the pressure reached a plateau, but this was less than one third the systolic pressure. The atrial pattern was not M-shaped, since the rise in pressure from the trough of the *y* descent to the next *c* wave was relatively gradual. There was little or no respiratory variation except in the depth of the *y* descent. Exercise doubled the right atrial pressure without significantly altering the pattern.

Although these findings were considered to be atypical for constrictive pericarditis, exploratory thoracotomy was advised. At operation no pericardial constriction or adhesions were found. The myocardium had a mottled gray appearance suggesting fibrosis. Both ventricles were enlarged and pulsated well.

After discharge the patient did fairly well at home for about 3 months, under his physician's care, but then developed increasing failure. Digitalis therapy was difficult because of various abnormal cardiac rhythms. The patient collapsed and died suddenly at home in October 1955.

At autopsy there were bilateral hydrothorax and ascites. Dense focal pericardial adhesions were found at the site of the previous exploration. The heart was hypertrophied and dilated in all chambers, weighing 580 Gm. There was diffuse fibrosis of the myocardium (fig. 4). There was no inflammation or active necrosis. The heart valves were normal. Other findings included an organized thrombus in the left atrium, an old infarct of the spleen and an organizing infarct of the left lower lobe of the lung, a small caseous tuberculous lesion of the right upper lobe of the lung, and portal cirrhosis of the liver. No conclusion was reached about the cause of the myocardial disease.

Case 3. The following case is presented briefly as a probable instance of myocardial fibrosis. M. H., a 48-year-old housewife, had had breathlessness and edema for 1 year. The edema had progressed to include the body wall and face. Her physician noted persistent albuminuria, but failed to induce improvement with digitalis, mercurial diuretics, and acetazoleamide (Diamox).

On examination she had generalized edema, a hoarse voice and dry skin. Cardiac enlargement and a soft precordial systolic murmur were noted. The pulmonic second sound was loud and split. There were a few rales at the left lung base. The blood pressure was 124/80. The liver was enlarged.

An electrocardiogram showed first degree A-V block (fig. 1). There was generalized cardiac enlargement with poor pulsations as judged from fluoroscopy, and hilar congestion, but no calcium (fig. 2). There was moderate albuminuria, and a serum albu-

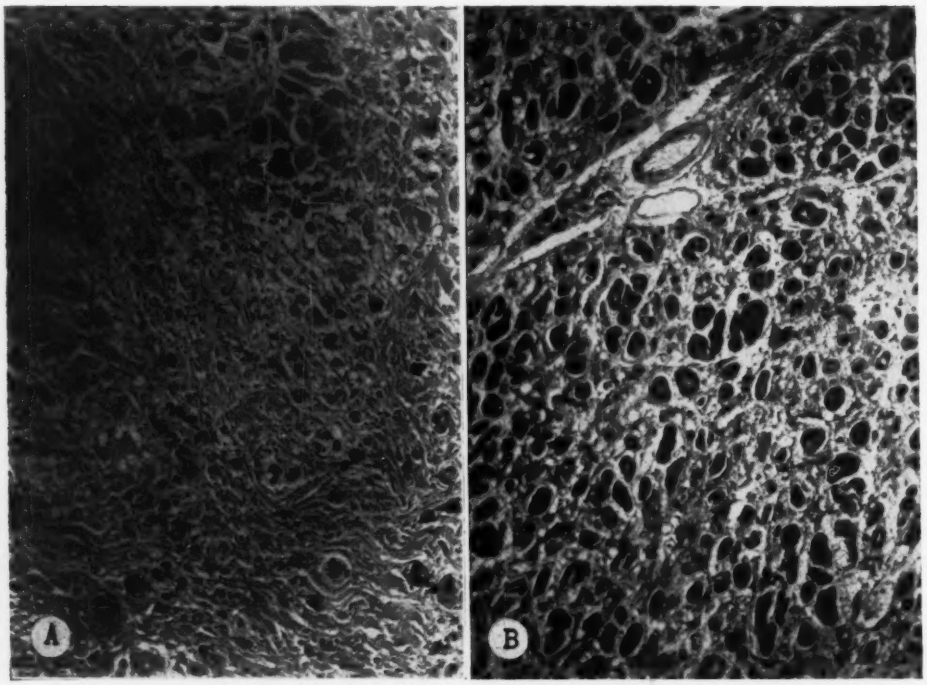


FIG. 4. Photomicrographs of sections through ventricular muscle of 2 patients with myocardial fibrosis, showing collagen deposition among the muscle fibers. *A*. Case 1, S. B. *B*. Case 2, E. K. × 100.

min/globulin ratio was 3·2/3·1. Other studies of renal, hepatic, and thyroid function were normal.

Cardiac catheterization (table 1 and fig. 3) revealed low cardiac output that did not rise with exercise. There was mild postcapillary pulmonary hypertension, also unaffected by exercise. The end-diastolic to systolic pressure ratio in the right ventricle was less than one third, and the dip went below the baseline in inspiration. The right atrial mean pressure was only mildly elevated, considering the degree of disability, and the contour showed considerable respiratory variation in amplitude.

At exploration, the pericardium was normal. The myocardium was pale, suggesting chronic myocarditis to the surgeon. The patient recovered satisfactorily from the operation, but 2 months later the failure began to increase rapidly and she died at home. No autopsy was performed.

DISCUSSION

Most authors have concluded that no reliable distinction can be made between myocardial fibrosis and constrictive pericarditis on the basis of the catheterization findings. This is not surprising, since the mode of production of the abnormal pulse contours is generally agreed to be the same in the 2 diseases. Indeed, similar abnormal patterns have also been reported in endocardial fibrosis,[9] funnel chest,[10] and pericardial tamponade.[4] In the 3 cases presented here, however, certain distinctions of a quantitative nature may be made, whose recognition may in the future save some, but not all, patients with myocardial fibrosis an unnecessary thoracotomy.

The following comparison is made with 6 cases of constrictive pericarditis studied by us,[3] since our findings are in general agreement with other published accounts of constrictive pericarditis.

First, the early diastolic dip in the right ventricular pressure tracings usually did not reach the atmospheric pressure baseline in constrictive pericarditis, (5 of our 6 cases) whereas it reached or went below the baseline in all our cases of myocardial fibrosis.

Second, the end-diastolic pressure in the right ventricle was equal to or above one third of the systolic pressure in all our cases with

onstrictive pericarditis. In only 1 of our patients with myocardial fibrosis did the diastolic pressure barely achieve this height, and then only in 1 or 2 out of several tracings.

Third, the right atrial mean pressure tended to be higher in patients with constrictive pericarditis than in those comparably disabled by myocardial fibrosis. Thus, 5 of our 6 patients with constrictive pericarditis had a mean right atrial pressure more than 16 mm. Hg. The sixth patient, whose right atrial mean pressure was 12 mm. Hg, was only mildly disabled. In contrast, the pressures in the fibrosis patients, all of whom were severely disabled, were only 10, 12, and 18 mm. Hg respectively.

Fourth, the right atrial pressure contour was less typical in fibrosis than in pericarditis. In the latter disease, the *y* descent was followed by a rapid upstroke and plateau, following the ventricular pattern and forming with the *x* descent the so-called W or M complex; and the only variation that occurred with respiration was a slight increase in the depth of the *y* descent during inspiration. In the patients with fibrosis, the respiratory variation in the depth of the *y* descent was slightly greater, and in 1 patient (case 3) there was also an increase in the positive deflections during inspiration, although the mean pressure did not fluctuate significantly. In another patient (case 2) whose ventricular pattern was not typical of constrictive pericarditis, the atrial pattern also contained a gradual, rather than an abrupt, rise after the *y* descent, so that the pattern came to resemble that seen in other types of severe heart failure.

To summarize the differential points, constrictive pericarditis should be strongly suspected when the right ventricular end-diastolic pressure is clearly and consistently one third the systolic or more, the early diastolic dip does not reach atmospheric pressure, the right atrial mean pressure is above 15 mm. Hg, there is little or no respiratory variation in mean atrial pressure or in the shape of the atrial pressure contour, and when there is an abrupt rise and high plateau after *y* descent, forming an atrial M or W complex. The less well these criteria are fulfilled, the more likely the lesion is to be myocardial fibrosis. Some overlapping may occur in either direction in some of these criteria, but we have not yet encountered a patient among our own cases or in the literature, with constrictive pericarditis, whose end-diastolic to systolic ratio in the right ventricle was less than one third. When this ratio is well below one third, therefore, myocardial fibrosis may be most strongly suspected. The converse is not always true, since Hetzel and co-workers[2] have presented tracings from a patient whose right ventricular pressure appears to be between 50 and 65 mm. Hg systolic and about 25 mm. Hg end-diastolic. The mean atrial pressure appears over 20 mm. Hg and does not vary with respiration. This patient was subjected to exploratory thoracotomy and the pericardium was found to be normal. No cause for the heart failure was discerned. Balchum, McCord, and Blount[4] and Sawyer and co-workers[11] have also presented proved cases of myocardial fibrosis with end-diastolic pressure in the right ventricle more than half the systolic.

The size of the heart, the vigor of its pulsations, and the absence of pericardial calcification cannot be relied on to distinguish between myocardial fibrosis and constrictive pericarditis, since many patients with proved constrictive pericarditis have cardiac enlargement without marked decrease in the amplitude of the beat and without calcification.

Summary

Three patients are presented with intractable heart failure. Two had proved myocardial fibrosis. The probable diagnosis of myocardial fibrosis in the third patient is based on the operative findings.

Many clinical and hemodynamic features strongly suggested constrictive pericarditis, particularly the right ventricular and right atrial pressure contours, although the pericardium was normal at operation.

The differentiation can sometimes be made on quantitative grounds. Severely disabled patients with right ventricular end-diastolic to systolic pressure ratios clearly less than one third, and with right atrial mean pressures well below 15 mm. Hg, are unlikely to have constrictive pericarditis. Any considerable respiratory variation in right atrial pressure contour

increases the likelihood that the diagnosis is myocardial fibrosis rather than constrictive pericarditis, as does the observation that the right ventricular early diastolic dip goes below the baseline. If these observations are confirmed and extended, it may become feasible to spare certain of these patients unnecessary thoracotomy. Patients with converse findings should be explored, even though cases of myocardial fibrosis will be included.

Summario in Interlingua

Es presentate tres patientes con intractabile disfallimento cardiac. Duo habeva demonstratemente fibrosis myocardial. In le tertie patiente le diagnose probabile de fibrosis myocardial es basate super le constatationes operatori.

Multe aspectos clinic e hemodynamic esseva forte indicios de pericarditis constrictive, specialmente le contornos del pression dextero-ventricular e dextero-atrial, ben que le pericardio esseva normal al operation.

Le differentiation pote a vices facer se super le base de factores quantitative. Severmente invalide patientes con proportiones inter le pression dextero-ventricular termino-diastolic e le pression systolic amontante a valores clarmente infra un tertio e con pressiones dextero-atrial medie amontante a valores clarmente infra 15 mm Hg non es probabile victimas de pericarditis constrictive. Omne grado considerabile de variation respiratori in le contorno del pression atrial augmenta le probabilitate que le diagnose deberea esser fibrosis myocardial plus tosto que pericarditis constrictive. Le mesmo es ver quando le depression initio-diastolic dextero-ventricular descende a infra le linea de base.

Si iste observationes es confirmate e extendite, il va forsan devenir possibile evitar thoracotomias innecessari in certes de iste patientes. Patientes con constatationes contrari deberea esser subjicite a operationes exploratori, mesmo si isto significa que casos con fibrosis myocardial es includite.

Acknowledgment

We are grateful to Dr. Roger Terry for the pathologic studies on case 1. We wish to express our appreciation and thanks to Dr. Morris Missal for the permission to study case 2, and to Dr. Milton G. Bohrod for the autopsy findings of the same case. We are indebted to Dr. Donald Jones for referring case 3 to us for study. Dr. E. B. Mahoney performed the exploratory thoracotomy on all 3 cases.

References

1 Bloomfield, R. A., Lauson, H. D., Cournand A., Breed, E. S., and Richards, D. W., Jr.: Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease. J. Clin. Invest. **25:** 639, 1946.

2 Hansen, A. T., Eskildsen, P., and Gotzsche H.: Pressure curves from the right auricle and the right ventricle in chronic constrictive pericarditis. Circulation **3:** 881, 1951.

3 Yu, P. N., Lovejoy, F. W., Jr., Joos, H. A., Nye, R. E., Jr., and Mahoney, E. B.: Right auricular and ventricular pressure patterns in constrictive pericarditis. Circulation **7:** 102, 1953.

4 Wilson, R. H., Hoseth, W., Sadoff, C., and Dempsey, M. E.: Pathologic physiology and diagnostic significance of the pressure pulse tracings in the heart in patients with constrictive pericarditis and pericardial effusion. Am. Heart J. **48:** 671, 1954.

5 Hetzel, P. S., Wood, E. H., and Burchell, H. B.: Pressure pulses in the right side of the heart in a case of amyloid disease and in a case of idiopathic heart failure simulating constrictive pericarditis. Proc. Staff Meet., Mayo Clin. **28:** 107, 1953.

6 Burwell, C. S., and Robin, E. D.: Some points in the diagnosis of myocardial fibrosis. Tr. A. Am. Physicians **67:** 67, 1954.

7 Balchum, O. J., McCord, M. C., and Blount, S. G., Jr.: The clinical and hemodynamic pattern in non-specific myocarditis: A comparison with other entities also impairing myocardial efficiency. Am. Heart J. **52:** 430, 1956.

8 Bruce, R. A., Lovejoy, F. W., Jr., Pearson, R., Yu, P. N., Brothers, G. B., and Velasquez, T.: Normal respiratory and circulatory pathways of adaptation in exercise. J. Clin. Invest. **28:** 1423, 1949.

9 Clark, G. M., Valentine, E., and Blount, S. G., Jr.: Endocardial fibrosis simulating constrictive pericarditis. New England J. Med. **245:** 349, 1956.

10 Lyons, H. A., Zuhdi, M. N., and Kelly, J. J., Jr.: Pectus excavatum ("funnel breast"), a cause of impaired ventricular distensibility as exhibited by right ventricular pressure pattern. Am. Heart J. **50:** 921, 1955.

11 Sawyer, C. G., Burwell, C. S., Dexter, L., Eppinger, E. C., Goodale, W. T., Gorlin, R., Harken, D. E., and Haynes, F. W.: Chronic constrictive pericarditis: further consideration of the pathologic physiology of the disease. Am. Heart J. **44:** 207, 1952.

Comparison of Fat Intake of American Men and Women

Possible Relationship to Incidence of Clinical Coronary Artery Disease

By MEYER FRIEDMAN, M.D., AND RAY H. ROSENMAN, M.D.

A detailed dietary survey of 46 women and their husbands belonging to an upper economic stratum was obtained. The caloric and percentage fat intakes of the sexes were almost identical. The data concerning the possible relationship of hormonal, dietary, and socioeconomic factors to the pathogenesis of coronary artery disease are reviewed.

RECENTLY a number of epidemiologic studies[1-6] have been published concerning the possible causes of the relative immunity of various classes and groups of non-American men against overt coronary artery disease. Since a low-fat intake was thought to be a trait common to all of these groups, it was concluded that this dietary habit was chiefly responsible for the observed relative infrequency of clinical coronary artery disease in these individuals.

Impressive as is this relative immunity of the poverty-stricken Bantu,[4, 5] the similarly stricken Southern Chinese,[7, 8] the economically depressed Italian[2] and Spaniard,[6] and similar groups against overt coronary disease, the immunity of the young, premenopausal American woman *of any class* is perhaps even more striking. Thus, before the age of 40, if she is neither hypertensive nor diabetic, she exhibits more than 20 times more resistance to symptomatic coronary disease than does her American male counterpart.[9-12]

In view of this truly astounding immunity of the young American female, it has seemed rather strange to us that no attempts, as far as we know, have been made to determine her daily fat intake. Yet if the reputed greater intake of fat on the part of her male counterpart (as compared to that of the non-American men referred to above) is held responsible by some observers[1-6] for his greater incidence of coronary artery disease, certainly her daily fat intake warrants scrutiny. Only in this manner can the possible relationship of fat intake to her immunity be assessed.

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The present article describes the results obtained in such a survey in which the dietary intakes of 46 women and their husbands were recorded and evaluated. These results indicate that the fat intake of both sexes is identical and hence the relative immunity against coronary disease to be expected in these women is due to other than dietary causes.

METHODS

Selection of Subjects. Volunteers of an upper class urban and suburban feminine social organization were selected for the present studies. They were married, below the age of 50 years, free of overt cardiovascular disease, and adjudged intelligent and reliable enough for the purposes desired. These women were provided with a printed protocol providing space for the detailed daily recording for 14 days, during November 1955, of their own and their husband's intake of all foods and beverages, both at regular mealtimes and otherwise. A standard but simple method of recording various solids and liquids was employed that seemed to make it simple for the subject to measure. In addition, information concerning the possible conscious restriction of caloric intake (i.e., dieting) was obtained.

Detailed instructions concerning the method of recording their food intake were given to these volunteers by the authors, in either group or personal interviews. During the latter, the general purpose of the research was explained to them so that their full cooperation in reporting food intakes honestly and accurately might be obtained. Such cooperation was more than satisfactory and we are as positive as one can be under the circumstances that the records chosen for the present study (46 of the 49 done) were meticulously assessed and recorded.

The dietary records thus compiled were submitted to 3 hospital dietitians who calculated from them, the total daily intake of calories, as well as the daily fractions of protein, carbohydrate, and fat.

RESULTS

Although the actual total caloric intake (1830) of the males of our group (table 1) was

TABLE 1.—*Daily Food Intake of Forty-Six Marital Pairs*

Sex	Av. age (yr.)	Av. weight (lb.)	Av. height (in.)	Average surface area ($M.^2$)	Conscious weight restriction (No.)	Average daily intake of food (caloric)				
						Total	Protein	Carbohydrate	Fat	Fat % of total intake
Male	38	173	71	1.98	20	1830	307	769	775	41
	(20–50)*	(130–226)	(67–77)	(1.62–2.39)		(967–2912)	(128–456)	(360–1328)	(376–1176)	(30–52)
Female	34	119	65	1.58	18	1577	256	645	665	42
	(20–50)	(100–165)	(60–71)	(1.4–1.94)		(804–2396)	(136–364)	(600–1068)	(376–1104)	(34–55)

*Range of values.

slightly greater than that of the females (1577), if these values are correlated to the body surface area of each group, that of the average male ($915/M.^2$), becomes somewhat less than that ($986/M.^2$) of the average female.

The daily fat intake of the men also was not found to be greater than that of their wives. Thus the daily fat intake of the males was 775 calories or 387 per $M.^2$ of surface area and that of the females was 665 calories or 409 per $M.^2$ of surface area. As table 1 shows, a similarity exists in the fractions of carbohydrate and protein ingested by each sex.

It was of interest that 18 of the women (39 per cent) and 20 of the men (44 per cent) were in the habit of consciously restricting their diet. This tendency of the members of the upper class to watch their weight and consequent intake of food should be an important factor to be reckoned with in any attempt to assess the food intake of any class or group by utilization of governmental statistics.

These dietary values obtained by us are considerably lower than those assumed to represent the average food intake of the well-nourished American citizen.[1, 2] However, these latter values have never been determined by direct survey but have been derived from government statistics[13] indicating only the amount of "food available for consumption." Such figures have at best a possible relevance for all classes and groups of the nation but it is extremely doubtful, in view of the present results, whether they are valid for a group of upper class, relatively sedentary Americans who rarely indulge in *continuous* heavy labor. Nevertheless, if there is to be a critical assessment of the dietary fat-atherosclerosis concept, the fat intake of this type of group may have more significance than a national survey embracing all groups because the male members of a group such as ours exhibit not an immunity but a proclivity to coronary artery disease.[14-16]

DISCUSSION

If these dietary results can be assumed to have national pertinency, then it is clear that the American, upper class, premenopausal female ingests as much or more fat than her male counterpart. In view of her known relative immunity to clinical coronary disease, these results suggest either that femaleness protects against the otherwise supposed atherogenic properties of a high-fat intake or else that a high-fat intake itself is not specifically or uniformly atherogenic. It therefore may be of profit to review some available evidence concerning both of these possibilities.

First, although there is no experimental evidence available from animal studies[17-19] that femaleness as such plays the slightest part in certain species in preventing atherosclerosis resulting from ingestion of diets high in fat and cholesterol, there is evidence[20] that administration of pharmacologic doses of estrogen protects the coronary vasculature of the chick against the atherogenic properties of a high cholesterol-high fat diet. However the production of hypopotassemia and nonreactivity to desoxycorticosterone acetate in these chicks[21] and possibly of associated hypotension[22] makes it questionable whether such data explain the striking immunity to clinical coronary disease of the American woman.[23, 24] Nor can estrogen entirely be credited for the relatively low β-lipoprotein content found in the premenopausal American female[23, 24] simply because

lowering of the β-lipoprotein content of men suffering from coronary artery disease can be accomplished by administration of *pharmacologic* doses of estrogen. The possible fallibility of such reasoning is emphasized by the fact that the rural Guatemalan female[13] (but not her urban compatriot) displays a high β-lipoprotein spectrum and this despite her undoubted abundance of female sex hormone. Before it therefore can be stated with assurance that either the femaleness or estrogen content of the American woman is responsible for her low plasma β-lipoprotein content, the blood of females of other groups and races both in and out of Western society must be analyzed.

Another reason presented as evidence that estrogen accounts for the relative immunity of the American woman against this disease is the supposed increase in its incidence after the menopause. However, examination of available statistics[25] suggests that similar to the male, there appears to be no sudden upsurge in the severity of coronary atherosclerosis in the American woman in the immediate postmenopausal years but a gradual and smoothly ascending increase from the fourth to the seventh decade. At all ages, however, the degree apparently remains less than that in the male.[25]

Secondly, protection against clinical coronary disease does not appear to be a sex-linked phenomenon in all races. Thus the American Negro woman completely lacks this protection[26] and, according to Keys,[27] the incidence of degenerative heart disease in Italy is about the same in both sexes.

Finally, it seems difficult to envision the striking immunity to this disease as due to the sex of the young American woman, if only because it dwindles considerably when she becomes hypertensive[28-31] and disappears entirely when she becomes diabetic.[32-34] Certainly a supposed protection of the potency of 20 to 1 afforded the American female before the age of 40,[9-12] might be expected to retain some influence in the face of these diseases.

These observations, when viewed as a whole, give little or no support to the belief that the American female may have a sex-linked protection against the atherogenic properties of a high-fat diet. This conclusion forces us to examine the second possibility, namely that a high-fat intake, *of and by itself*, is not specifically responsible either for the greater incidence of *clinical* coronary disease in the American male as compared to the American female or to men of other groups ingesting lower amounts of fat, or for their supposed higher level of serum cholesterol and β-lipoproteins.

Several authors[1-6, 27] have presented data suggesting that the male members of certain groups of various countries and races[2, 4-8, 35-42] ingesting low amounts of fat (10 to 20 per cent of the total caloric intake) also show a markedly lower incidence of deaths due to coronary artery disease and its complications (i.e., thrombosis and myocardial infarction) as well as lower levels of serum cholesterol and β-lipoproteins. It also has been pointed out that ingestion of excess fat when given with cholesterol accelerates processes of hypercholesteremia and atherosclerosis in the chick,[43] rat,[44] rabbit,[45] and monkey.[19] These epidemiologic and experimental observations have been emphasized recently by some investigators[1-6] as support for their belief in the role of dietary fat in the pathogenesis of coronary artery disease.

Critical analysis however of the above data and of *other existing data* not taken into consideration or emphasized by these dietary proponents, leads the impartial observer to believe that the differences found in the incidence of clinical coronary disease in various groups and races cannot be ascribed with certainty only to differences in the increment of fat ingested. This conclusion was reached for the following reasons.

First, much dietary data now used to incriminate a high-fat intake in the pathogenesis of coronary artery disease were not obtained by detailed, systematically conducted food diaries but were interpolated from governmental statistics. As Mann, Munoz, and Scrimshaw[13] have pointed out, the usual dependence upon such data may lead to considerable error. Indeed our own survey and that of Davis and Scoular[46] indicate that among supposedly well-nourished persons, the actual dietary intake was only one half that

which could be deduced from statistics of the U. S. Department of Agriculture[13] on "foods available for consumption."

Secondly, it is claimed that a low-fat intake possibly protects against coronary artery disease by lowering plasma cholesterol.[1-6, 27] However, it is to be doubted quite seriously whether only a low-fat intake is per se responsible for the lower plasma cholesterol observed in relatively immune groups and races. This is so, not only because plasma cholesterol is not consistently lowered[47] by a low-fat intake, but it can even be increased by augmenting the protein or carbohydrate fractions of the diet.[48] Indeed, plasma cholesterol can even rise if physical activity is curtailed.[49] Furthermore, the "low fat intake-low plasma cholesterol" concept fails to explain the low plasma cholesterol of the Navajo who eats as much animal fat as the average American white man.[50-52] Indeed, when the plasma cholesterol of United States citizens ingesting 40 per cent of the diet as fat[13, 50, 52] is compared with that of Italian males ingesting only half as much fat,[2] it is actually extremely doubtful if a statistically significant (not to mention a physiologically significant) difference can be shown to exist. These facts appear to us to negate the possible over-all inevitability of "low fat intake-low plasma cholesterol" relationship. Actually the basic mechanism responsible for the plasma cholesterol level remains unknown.

Thirdly, it has been proposed[1-6] that a high-fat intake per se leads to a higher concentration of plasma β-lipoprotein, but this appears untenable in view of recent evidence that complete dissociation may exist not only between intake of fat and the level of β-lipoproteins, but also between serum levels of cholesterol and β-lipoproteins.[13, 19, 44, 46, 49, 50] Actually it would appear that the serum β-lipoprotein content, similar to the cholesterol level, may be determined by factors other than just fat intake.[13, 19, 47-49]

Fourthly, with possible exception of the Bantu,[4, 5] epidemiologists have not stressed the relative infrequency of hypertension that also has been observed[27, 38, 42, 53-58] in their low-fat-eating groups found relatively immune to heart disease. In view of the well-known association between hypertension and augmentation of coronary disease,[28-31, 59] their failure to consider this second peculiarity of these immune persons makes their final conclusions open to doubt.

Fifthly, almost all of the relatively immune groups, classes, and races studied, besides ingesting less fat, also indulge in considerably more physical exertion than American groups with whom they were compared. This difference, although seemingly discarded by some observers,[3-5] nevertheless may have considerable influence upon the incidence of coronary disease in the groups compared.[60]

Sixthly, mortality statistics and not data obtained by pathologic study frequently have been used to determine the incidence or prevalence of coronary artery disease in epidemiologic studies.[1-6] However, deaths due to myocardial infarction cannot be employed necessarily as an index of the respective incidence of coronary artery disease in various groups. Thus the abrupt decline in cardiac deaths in Norway occurred in a matter of a few months,[42, 61] a phenomenon that cannot be ascribed to any unique resolution of coronary atherosclerosis itself. Moreover, there was a similar decline in deaths due to other types of heart disease and also just as marked a decline in postoperative deaths following pelvic surgery in females.[41, 42]

Actually coronary atherosclerosis may be almost ubiquitous in men of Western society, but myocardial infarction is a sudden affliction of a minority.[62] This latter concept also is borne out by the recent study of Morris[63] who noted a 7-fold increase in the incidence of deaths due to coronary disease in English persons from 1907 to 1949 although an actual decrease occurred in the incidence of advanced coronary atheromatosis in the same population. This dissociation of morbidity and mortality is also found to a lesser extent in the Bantu and the Melanesians.[4, 5, 64-66]

These latter findings suggest that if a high-fat intake does increase the *death rate* due to coronary heart disease, it may do so, not by increasing the degree of atherosclerosis as such, but by increasing the incidence of thrombotic complications by inducing changes in blood

coagulation,[67-72] clumping of red blood cells,[73-75] and possible capillary obstruction by chylomicra,[76-78] which, when superimposed upon the basic coronary disease, increase its lethality.

Seventhly, as we have previously pointed out,[79] the fat intake of several races[19, 50-52, 79, 80] is comparable to that of the middle or upper class American, yet their incidence of coronary artery disease is almost nonexistent. Nor can these exceptions be dismissed as due to hereditary influences. The high incidence of coronary artery disease in the American Jew has been so explained by some observers,[81] but the immunity of the non-Westernized Yemenite Jew[39] makes it necessary to adopt extreme caution before an hereditary protection is promulgated to explain glaring deviations from an arbitrarily erected concept.

Finally, it should be pointed out that in most epidemiologic studies, little attention has been paid to the really striking fact that immune groups invariably have belonged to either the lower socioeconomic class of Western society or to groups not belonging to this society. Conversely stated, only middle and upper class Western man has this disease in abundance.

As we have previously emphasized,[79] the American executive differs from these immune groups in more than just dietary respects. One of the outstanding differences is his exposure to, indeed his immersion in, the rapidly increasing profound emotional stresses and tensions of this society. A succinct description of this emotional stress was given by de Tocqueville as early as 1836[82] and it was allied with coronary artery disease by Osler in 1899[83] and by Stewart in 1950.[84] Indeed, the physiologic and pathologic effects of the application of this stress have begun to be recorded.[85-90] Nevertheless, its possible importance has been brought up in epidemiologic studies only to be summarily dismissed.[3, 91]

Despite the negation of emotional stress by its neglect, if its absence in a group is used as a standard of comparison, as good or perhaps a better correlation can be obtained with it and the decreased incidence of coronary artery disease[4, 5, 14, 15] as can be obtained with a low-fat intake. Thus, absence of socioeconomic stress in the placid Navajo[92] and Eskimo[93-95] correlates with their rarity of coronary artery disease, whereas no such correlation could be found if their fat intake were employed as a standard. Again as Brock and Bronte-Stewart[4, 5] pointed out in their studies in Cape Town, if job responsibility were used as an index, as good a correlation could be found between it and the increased incidence of coronary artery disease as was found with the fat intake.

In the same regard, it should be mentioned that, both in the study of Gertler and White[9] and that of Yater and co-workers,[96] although no difference was found between the dietary habits of their young coronary patients and those of the controls, considerable difference was found in the type of civil positions held by the 2 groups. The young coronary patient almost always had occupied a position demanding responsibility and frequently associated with emotional stress.

In view of these observations, it seems almost incredible that a factor so rampant in the American community has received so little considered objective attention. How can one compare the incidence of a disease (whose etiology is obscure) in the American male with that in the American housewife, the male eunuch, the Chinese coolie, or the Bantu without giving as much weight to this factor of "socioeconomic stress" as to any other factor? Undoubtedly the measurement of the dietary fat intake of a group of persons is infinitely easier than a similar evaluation of their socioeconomic stresses. Such difficulty, however, should not lead us to assume that the latter may not be an important factor. The forces of nature unfortunately are not yet applied according to the ease with which we can discover and understand them, much less measure them.

Summary

A detailed dietary history was obtained of 46 women and their husbands, belonging to an upper economic stratum. No significant difference was found in the caloric or percentage fat intake of each sex, when corrected for differences in surface area.

A critical review of various data relating to the relative immunity of the American woman to clinical coronary artery disease suggests that this immunity cannot be due entirely to some endocrine-induced protection against the supposed atherogenic properties of a high-fat dietary.

A similar review was made of the data relating the high intake of fat to the increased incidence of clinical coronary artery disease as observed in the American male. It was concluded that such a relationship is not only unproved but probably untenable.

The possible atherogenic potential of the socioeconomic stress peculiar to and characteristic of the middle and upper class male of Western society is discussed.

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Summario in Interlingua

Esseva obtenite un detaliate historia dietari de 46 feminas e lor sposos pertinente a un strato economic superior. Nulle significative differentias inter le sexos esseva constatate in le ingestion caloric o procentual de grassia post compensation del valores pro differentias in le areas de superficie corporee.

Un revista critic del varie datos concernente le immunitate relative de feminas american contra clinic morbo de arteria coronari pare indicar que iste immunitate non pote esser le effecto de alicun protection de origine endocrin contra le proprietates supponitemente atherogene de dietas ric in grassia.

Un simile revista esseva facite pro le datos concernente le stipulate relation inter alte valores del ingestion de grassia e le augmentate incidentia de clinic morbo de arteria coronari observate in le masculo american. Le conclusion esseva que iste relation es non solmente non demonstrate sed probabilemente etiam non tenibile.

Es discutite le possibile potential atherogene del stresses socio-economic que es un characteristica particular del masculo del classes medie e superior in le societate occidental.

REFERENCES

[1] Keys, A.: Atherosclerosis: A problem in newer public health. J. Mt. Sinai Hosp. **20:** 118, 1953.

[2] —, Fidanza, F., Scardi, V., Bergami, G., Keys, M. H., and Di Lorenzo, F.: Studies on serum cholesterol and other characteristics of clinically healthy men in Naples. Arch. Int. Med. **93:** 328, 1954.

[3] —: Mode of life and the prevalence of coronary heart disease. Symposium on Arteriosclerosis of the Minnesota Heart Association, Sept. 1955, page 28.

[4] Brock, J. F., and Bronte-Stewart, B.: Arteriosclerosis in African populations. Symposium on Arteriosclerosis of the Minnesota Heart Assoc., Sept. 1955, page 102.

[5] Bronte-Stewart, B., Keys, A., and Brock, J. F.: Serum cholesterol, diet, and coronary heart disease: An inter-racial survey in the Cape Peninsula. Lancet **2:** 1103, 1955.

[6] Keys, A., Vivanco, F., Rodriguez-Minon, J. L., Keys, M. H., and Castro-Mendozo, H.: Studies on the diet, body fatness and serum cholesterol in Spain. Metabolism **3:** 195, 1954.

[7] Rosenthal, S. R.: Studies in atherosclerosis: Chemical, experimental and morphologic, I and II, III and IV. Roles of cholesterol metabolism, blood pressure and structure of aorta; fat angle of aorta (F.A.A.), and infiltration-expression theory of lipoid deposit. Arch. Path. **18:** 473, 660, 1934.

[8] Snapper, I.: Chinese Lessons to Western Medicine. New York, Interscience, 1941.

[9] Gertler, M. M., and White, P. D.: Coronary Heart Disease in Young Adults: A Multidisciplinary Study. Cambridge, Harvard University Press, 1954.

[10] Jones, H. B., Gofman, J. W., Lindgren, F. T., Lyon, T. P., Graham, D. M., Strisower, B., and Nichols, A. V.: Lipoproteins in atherosclerosis. Am. J. Med. **11:** 358, 1951.

[11] Glendy, R. E., Levine, S. A., and White, P. D.: Coronary disease in youth: Comparison of 100 patients under 40 with 300 persons past 80. J. A. M. A. **109:** 1775, 1937.

[12] Clawson, B. J., and Bell, E. T.: Incidence of fatal coronary disease in nondiabetic and in diabetic persons. Arch. Path. **48:** 105, 1949.

[13] Mann, G. V., Munoz, J. A., and Scrimshaw, N. S.: The serum lipo-protein and cholesterol concentrations of Central and North Americans with different dietary habits. Am. J. Med. **19:** 25, 1955.

[14] Ryle, J. A., and Russell, W. T.: The natural history of coronary disease: A clinical and

epidemiological study. Brit. Heart J. **11:** 370, 1949.

[15] Registrar-General, Decennial Supplement, England and Wales, 1951, Occupational Mortality, London: H. M. Stationery Office, Part 1, page 13.

[16] Cardiovascular Disease: Data on Mortality, Prevalence and Control Activities. Public Health Service Publication No. 429, U. S. Dept. of Public Health, Education and Welfare, 1955.

[17] Stamler, J., Pick, R., and Katz, L. N.: Further studies on estrogen prophylaxis of cholesterol-induced coronary atherogenesis. Circulation **8:** 436, 1953.

[18] Mininni, G., Contro, S., and Checchia, C.: Effects of ovariectomy on experimental atherosclerosis in rabbits. Circulation **8:** 452, 1953.

[19] Mann, G. V., and Stare, F. J.: Nutrition and Atherosclerosis. Symposium on Atherosclerosis. Publication 338 of National Academy of Science, Washington, 1954, p. 169.

[20] Katz, L. N., and Stamler, J.: Experimental Atherosclerosis. Springfield, Ill., Charles C Thomas, 1953.

[21] Stamler, J.: Estrogen inhibition of corticoid hypertension in chickens. Circulation **10:** 896, 1954.

[22] Freed, S. C., Rosenman, R. H., and Friedman, M.: The relationship of potassium in the regulation of the blood pressure with special attention to corticosteroid hypertension. New York Acad. Sc. **56:** 637, 1953.

[23] Russ, E. M., Eder, H. A., and Barr, D. P.: Influence of gonadal hormones on protein-lipid relationships in human plasma. Am. J. Med. **19:** 4, 1955.

[24] Barr, D. P.: Hormonal Factors in the Pathogenesis of Atherosclerosis. Symposium on Arteriosclerosis of the Minnesota Heart Assoc., Sept. 1955, p. 58.

[25] Ackerman, R. F., Dry, T. J., and Edwards, J. E.: Relationship of various factors to the degree of coronary atherosclerosis in women. Circulation **1:** 1345, 1950.

[26] Keil, P. G., and McVay, L. V.: A comparative study of myocardial infarction in the white and Negro races. Circulation **13:** 712, 1956.

[27] Keys, A.: Symposium on Atherosclerosis, Publication 338 of National Academy of Sciences, Washington, 1954.

[28] Smith, D. E., Odel, H. E., and Kernohan, J. W. Causes of death in hypertension. Am. J. Med. **9:** 516, 1950.

[29] Davis, D., and Klainer, M. J.: Hypertensive heart disease; incidence of coronary atherosclerosis in cases of essential hypertension. Am. Heart J. **19:** 185, 1940.

[30] Master, A. M.: Hypertension and coronary occlusion. Circulation **8:** 170, 1953.

[31] Zeman, F. C., and Schwartz, B. M.: The effect of arteriosclerosis on the dynamics of hypertension in the aged. J. Gerontol. **3:** 40, 1948.

[32] Liebow, I. M., and Hellerstein, H. K.: Cardiac complications in diabetes mellitus. Am. J. Med. **7:** 660, 1949.

[33] —, —, and Miller, M.: Arteriosclerotic heart disease in diabetes mellitus: A clinical study of 383 patients. Am. J. Med. **18:** 438, 1955.

[34] Ricketts, H. T.: The problem of degenerative vascular disease in diabetes. Am. J. Med. **19:** 933, 1955.

[35] Steiner, P.: Necropsies on Okinawans. Arch. Path. **42:** 359, 1946.

[36] Benjamin, E. L.: Report of two hundred necropsies on natives of Okinawa. U. S. Naval Med. Bull. **46:** 495, 1946.

[37] Wilens, S. L.: Bearing of general nutritional status on atherosclerosis. Arch. Int. Med. **79:** 129, 1947.

[38] Chavez, I.: The incidence of heart disease in Mexico. Am. Heart J. **24:** 88, 1942.

[39] Dreyfuss, E.: The incidence of myocardial infarction in various communities in Israel. Am. Heart J. **45:** 749, 1953.

[40] Malmros, H.: The relation of nutrition to health. A statistical study of the effect of wartime on arteriosclerosis, cardiosclerosis, tuberculosis and diabetes. Acta. med. scandinav. Suppl. **246:** 137, 1950.

[41] Dedichen, J., Ström, A., Adelsten-Jensen, R., and Closs, K.: Incidence of atherosclerosis disease during war years. *In* Factors Regulating Blood Pressure. Josiah Macy, Jr. Foundation, New York, 1951.

[42] Ström, A., and Jensen, R. A.: Mortality from circulatory diseases in Norway, 1940–1945. Lancet **1:** 126, 1951.

[43] Pick, R., Katz, L. N., Rodbard, S., and Stamler, J.: Influences of neutral fat and plant sterols on exogenous and endogenous hypercholesterolemia and hyperphospholipemia in chicks. Circulation **10:** 610, 1954.

[44] Malinow, M. R., Hojman, D., and Pellegrino, A. A.: Production of atherosclerosis in the rat, an omnivorous animal, by forced feeding of vegetable oil. Circulation **10:** 592, 1954.

[45] Anitschkow, N.: Dan Wesen und die Entstehung der Atherosklerose. Ergebn. d. inn. Med. u. Kinderh. **28:** 1, 1925.

[46] Davis, A. N., and Scoular, F. I.: Caloric values of self-selected diets of young college women. Abstract No. 28 of papers presented at the American Chemical Society, Dallas meeting, April, 1956.

[47] Hatch, F. T., Abell, L. L., and Kendall, F. E.: Effects of restriction of dietary fat and cholesterol upon serum lipids and lipoproteins in patients with hypertension. Am. J. Med. **19:** 48, 1955.

[48] WALKER, W. J., LAWRY, E. Y., LOVE, D. E., MANN, G. V., LEVINE, S. A., AND STARE, F. J.: Effect of weight reduction and caloric balance on serum lipoprotein and cholesterol levels. Am. J. Med. **14:** 654, 1953.

[49] STARE, F. J.: Paper presented at 1956 Graduate Symposium on Geriatric Medicine of the American Geriatric Society, New York.

[50] LEWIS, L. A.: The lipoprotein system. Symposium on Arteriosclerosis of Minnesota Heart Assoc., Sept., 1955, p. 45.

[51] GILBERT, J.: The absence of coronary thrombosis among a select group. Bull. California Heart Assoc., May, 1954.

[52] PAGE, I. H., LEWIS, L. A., AND GILBERT, J.: Plasma lipids and proteins and their relationship to coronary disease among Navajo Indians. Circulation **13:** 675, 1956.

[53] MARVIN, H. P., AND SMITH, E. R.: Hypertensive cardiovascular disease in Panamanians and West Indians residing in Panama and the Canal Zone. Mil. Surgeon **91:** 529, 1942.

[54] CODBURY, W. W.: Blood pressure of normal Cantonese students. Chinese M. J. **37:** 715, 823, 1923.

[55] FOSTER, J. H.: The practice of medicine in China and New England with observations on hypertension. New England J. Med. **203:** 1073, 1930.

[56] —: Blood pressure of foreigners in China. Arch. Int. Med. **40:** 38, 1927.

[57] KRAKOWER, A.: Blood pressure of Chinese living in Eastern Canada. Am. Heart J. **9:** 396, 1934.

[58] LING, W. K.: The blood pressure of the Chinese: A statistical study of 20,948 life insurance applicants. Chinese M. J. **50:** 1773, 1936.

[59] TOBIAN, L.: Hypertension and atherosclerosis. Symposium on Arteriosclerosis of Minnesota Heart Assoc., Sept., 1955, p. 54.

[60] MORRIS, J. N., HEADY, J. A., RAFFLE, P. A. B., ROBERT, C. G., AND PARKS, J. W.: Coronary heart disease of physical activity of work. Lancet **2:** 1053, 1111, 1953.

[61] PIHL, A.: Cholesterol studies. II. Dietary cholesterol and atherosclerosis. Scandinav. J. Clin. & Lab. Invest. **4:** 122, 1952.

[62] EDITORIAL. Coronary Artery Disease. Lancet **2:** 1123, 1955.

[63] MORRIS, J. N.: Recent history of coronary disease. Lancet **1:** 1, 1951.

[64] HYMAN, A. S.: Heart disease in the jungles of the South Pacific: Some observations made among the Melanesians of the New Hebrides and Solomon Islands area. Ann. Int. Med. **22:** 639, 1945.

[65] BECKER, B. J. P.: Cardiovascular disease in the Bantu and coloured races of South Africa. South African J. M. Sc. **11:** 97, 107, 1946.

[66] ELLIOTT, G. A.: The coronary arteries and their diseases in the Bantu. Leech **23:** 25, 1953.

[67] EDITORIAL: Fat and Thrombosis. Brit. M. J. **1:** 973, 1954.

[68] DUNCAN, J. C., AND WALDRON, J. M.: The effect of ingested fat on blood coagulation. Tr. A. Am. Physicians **42:** 179, 1949.

[69] WALDRON, J. M., BIEDELMAN, B., AND DUNCAN, G. G.: The local and systemic effects of cream on blood coagulation. Gastroenterology **17:** 360, 1951.

[70] FULLERTON, H. W., DAVIE, W. J. A., AND ANASTOPOULOS, G.: Relationship of alimentary lipemia to blood coagulation. Brit. M. J. **2:** 250, 1953.

[71] VANDENBROUCKE, J., LAUVERS, P., AND VERSTRAETE, M.: International Congress Hematology Communication No. 129, 1954.

[72] POOLE, J. C. F.: The significance of chylomicra in blood coagulation. Brit. J. Haematol. **1:** 229, 1955.

[73] CULLEN, C. F., AND SWANK, R. L.: Intravascular aggregation and adhesiveness of the blood elements associated with alimentary lipemia and injections of large molecular substances. Circulation **9:** 335, 1954.

[74] SWANK, R. L.: Changes in blood produced by a fat meal and by i.v. heparin. Am. J. Physiol. **164:** 798, 1951.

[75] —: Effect of high fat feedings on viscosity of the blood. Science **120:** 427, 1954.

[76] KUO, P. T., AND JOYNER, C. R.: Angina pectoris induced by fat ingestion in patients with coronary artery disease. J.A.M.A. **158:** 1008, 1955.

[77] —, AND —: Relief of lipemia-induced angina pectoris by intravenous heparin. Circulation **12:** 735, 1955.

[78] ANDERSON, N. G., AND FAWCETT, B.: An anti-chylomicronemic substance produced by heparin. Proc. Soc. Exper. Biol. & Med. **74:** 768, 1950.

[79] FRIEDMAN, M., ROSENMAN, R. H., AND BYERS, S. O.: Deranged cholesterol metabolism and its possible relationship to human atherosclerosis: A review. J. Gerontol. **10:** 60, 1955.

[80] GARN, S. M., AND GERTLER, M. M.: Age and sex differences in serum cholesterol of Aleutians. Canad. M. A. J. **64:** 338, 1951.

[81] GLASS, B.: Anatomical and biochemical aspects of heredity in reference to atherosclerosis. Symposium on Atherosclerosis, Publication 338. of National Academy of Sciences, Washington, 1954, p. 7.

[82] DE TOCQUEVILLE, A.: Democracy in America. New York, D. Appleton & Co., 1904.

[83] OSLER, W.: Lectures on Angina Pectoris and Allied States. New York, D. Appleton & Co., 1897.

[84] STEWART, I. McD. G.: Coronary disease and modern stress. Lancet **2:** 867, 1950.

[85] GARB, S.: The current status of anti-coagulants in

the treatment of myocardial infarction. Am. J. M. Sc. **229:** 534, 1955.

[86] KUHL, W. J., BECK, E. M., GERSHBERG, H., STREET, E., AND RALLI, E. P.: Effect of cold water stress on blood and urine constituents in 55 normal male subjects. Metabolism **4:** 143, 1955.

[87] BRONTE-STEWART, B., AND HEPTINSTALL, R. H.: The relationship between experimental hypertension and cholesterol-induced atheroma in rabbits. J. Path. & Bact. **68:** 407, 1954.

[88] WILENS, S. C.: The effect of postural hypertension on the development of atheromatosis in rabbits fed cholesterol. Am. J. Path. **19:** 293, 1943.

[89] WHITE, P. D.: The psyche and the soma. Ann. Int. Med. **35:** 1291, 1951.

[90] JACOBSON, E.: Principles underlying coronary heart disease: Considerations for a working hypothesis. Cardiologia **26:** 83 (Fasc. 2), 1955.

[91] ARNOTT, W. M.: The changing aetiology of heart disease. Lancet **1:** 1251, 1954.

[92] COHEN, B. M.: Arterial hypertension among indians of the Southwestern United States. Am. J. M. Sc. **225:** 505, 1953.

[93] THOMAS, W. A.: Health of a carnivorous race: A study of the Eskimo. J.A.M.A. **88:** 1559, 1927.

[94] ALEXANDER, F.: A medical survey of the Aleutian Islands (1948). New England J. Med. **240:** 1035, 1949.

[95] ESKIMO. Encyclopaedia Britiannica **9:** 769, 13th. Ed., 1926, London, Encyclopaedia Britannica Co., Ltd.

[96] YATER, W. M., TRAUM, A. H., BROWN, W. G., FITZGERALD, R. P., GEISLER, M. A., AND WILCOX, B. B.: Coronary artery disease in men eighteen to thirty-nine years of age. Am. Heart J. **36:** 334, 481, 683, 1948.

Snow, P. J. D., Jones, A. M., and Daber, K. S.: A Clinico-pathological Study of Coronary Disease. Brit. Heart J. **18:** 435 (Oct.), 1956.

Clinical and pathologic findings were correlated in 32 patients who developed clinical evidence of ischemic heart disease within 3 months of death. Of 53 coronary occlusions, only 7 were not followed by myocardial infarctions. The occlusions occurred in vessels supplying muscle previously infarcted. Of 77 infarcts, 52 were recent. Twenty-eight patients had ischemic pain longer than 30 minutes, 2 angina pectoris, 2 aggravation of dyspnea, and 19 had no apparent symptoms. Painless myocardial infarction usually occurs in patients who do not have coronary occlusion. The authors believe that pain may be due to the intensity of the ischemia (greatest when a vessel is occluded) and infarction due to the duration of ischemia. There is no evidence that coronary occlusion without infarction causes symptoms.

SOLOFF

Electrocardiogram and Vectorcardiogram in Right Ventricular Hypertrophy and Right Bundle-Branch Block

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Electrocardiographic and vectorcardiographic studies on normal subjects and patients with heart disease suggest that criteria for the diagnosis of right ventricular hypertrophy can be improved and simplified. This report proposes new criteria for the electrocardiographic diagnosis of right ventricular hypertrophy. These criteria decrease the incidence of "false negative" and "false positive" interpretations, and also make possible the recognition of right ventricular hypertrophy in the presence of the $R' - V_1$ pattern, provided the QRS duration is less than 0.12 second. The findings and limitations of vectorcardiography in right ventricular hypertrophy and "right bundle-branch block" are discussed.

THE earliest and most reliable signs of right ventricular hypertrophy are the characteristic changes in the electric field of the heart, which are reflected in the conventional leads of the scalar electrocardiogram. The investigation reported here was undertaken in the hope that present criteria for the electrocardiographic diagnosis of right ventricular hypertrophy[1, 2] could be improved so as to identify correctly a larger proportion of cases in which right ventricular hypertrophy is present, reduce the number of false positives in normal subjects, and allow interpretation of records that show an R′ in lead V_1.

Electrocardiographic and vectorcardiographic study of normal persons[3] and patients with heart disease showed that the most important and characteristic electric change produced by right ventricular hypertrophy is the shift of the spatial QRS axis rightward and anteriorly. We therefore adopted tentatively the following criteria, which depend only on the QRS complex in lead V_1 and the frontal plane QRS axis: QRS duration less than 0.12 second, and either: (1) Mean frontal plane QRS axis between $+110°$ and $\pm 180°$, or between $-91°$ and $\pm 180°$; *or* (2) R/S or R′/S ratio in V_1 greater than 1.0, with R or R′ greater than 0.5 mv. In calculating mean QRS axis for this purpose the method of Carter, Richter, and Greene[4] was used. The smallest polar angle between the values given is the one that applies.

These criteria were applied to a consecutive series of electrocardiograms recorded on routine hospital patients, to test the number of false positives that would result, and to another series of records from patients with autopsy-confirmed right ventricular hypertrophy, to estimate the incidence of false negatives. Spatial vectorcardiograms were investigated in selected patients, to see what additional information might be provided by this technic.

METHODS AND PATIENT SELECTION

Normal series. This group of 103 persons has been described elsewhere.[3] It included 64 males and 39 females, ranging in age from 10 to 70 years. Electrocardiograms on these subjects were recorded on a 4-channel Hathaway S-14C oscillograph,* with amplifiers constructed in our laboratory.[5] Frequency response of this recording system is linear to at least 180 c.p.s., down 5 per cent at 200 c.p.s. and 50 per cent at 275 c.p.s. A time constant of 2.7 seconds determines the low frequency response. Time intervals can be measured accurately to 0.0025 second. Standard bipolar and unipolar limb leads, and chest leads V_{6R}, V_{3R}, and V_1 to V_6 were recorded. A simultaneous lead II was recorded with all other leads as a timing reference.

Heart Station Series. Electrocardiograms recorded on consecutive patients in the Johns Hopkins Hos-

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* Hathaway Instruments Co., Denver, Colo.

pital Heart Station during a period of 18 months were reviewed. Records were selected for further study if they satisfied the criteria previously described for the diagnosis of right ventricular hypertrophy, or if the QRS duration were 0.12 second or more with the pattern of right bundle-branch block in lead V_1. All diagnostic information available on 71 patients thus selected was reviewed, including history, physical findings, laboratory tests, roentgenograms, and other pertinent special studies, excluding the electrocardiographic interpretation. Patients were then eliminated from the series if the evidence available was inadequate to make a reasonably certain diagnosis (5 patients), if there was evidence of both coronary disease and a disease that would lead to right ventricular hypertrophy (17 patients), or if they were over the age of 50 years (3 patients), even though no evidence of heart disease was found. Twenty-five patients were thus excluded in an effort to arrive at a group with relatively well-established diagnoses that could be divided without overlapping into normal subjects, patients with cardiac lesions that produce right ventricular hypertrophy, and patients with coronary artery disease. We had planned also to eliminate cases with disease that would lead to isolated left ventricular hypertrophy, but none was found in this group. Some of the rheumatic and congenital cases doubtless had combined right and left ventricular hypertrophy, but the clinical evidence indicated that the burden was predominantly right-sided in all cases. Two of the 18 cases with coronary disease also had arterial hypertension.

The 46 remaining cases are summarized in table 2. One person had no demonstrable heart disease, 18 patients had coronary artery disease (4 with a history of previous myocardial infarction), 17 patients had rheumatic heart disease with predominant mitral stenosis, 9 patients had congenital heart disease, and there was 1 case of chronic cor pulmonale.

Autopsy Series. Autopsy records of the Johns Hopkins Hospital over a period of 33 months were reviewed. Out of 1922 autopsies performed during that period, 48 cases over the age of 1 year had definite right ventricular hypertrophy without complicating left ventricular hypertrophy or myocardial disease due to coronary obstruction. Requirements for the anatomic diagnosis of right ventricular hypertrophy were heart weight more than 25 per cent over normal average for body weight and sex,[6] and right ventricular thickness greater than 4 mm. Only those cases that satisfied both requirements were included.

In 32 of these 48 cases, electrocardiograms were taken within 9 months of death that included at least 3 limb leads and 3 precordial leads. In 24 cases electrocardiograms had been recorded less than 1 week before death.

Vectorcardiographic Series. Spatial vectorcardiograms were recorded on a total of 67 patients whose scalar electrocardiograms either met the proposed criteria or showed a QRS duration of 0.12 second or more but otherwise met these criteria. On the same grounds for exclusion described above, 7 of these patients were eliminated because of insufficient evidence to establish a diagnosis, 1 case because of combined coronary disease and right ventricular hypertrophy, and 5 because of age over 50 years, leaving a total of 54 patients.

Vectorcardiograms were recorded with a cubical lead system and apparatus described previously.[3, 5] Scalar records of the x, y, and z components of the spatial vectorcardiogram were used to aid in the interpretation of the vectorcardiographic loops.

Definitions. 1. R/S ratio: the ratio of the amplitude of the tallest single positive deflection in a lead(numerator) to that of the deepest negative deflection in the same lead(denominator). Amplitudes are measured from the P-Q segment.

2. R′: the second of 2 positive components of a QRS complex that are separated by a downward deflection that reaches or crosses the iso-electric line.

3. Complete right bundle-branch block (RBBB): QRS duration 0.12 second or more, with a positive late deflection in lead V_1 and a negative late deflection in lead I.

4. Mean QRS axis: mean manifest frontal plane QRS axis calculated from the nomogram of Carter, Richter, and Green,[4] (not by the more accurate method of measuring the area beneath each deflection). This axis is not necessarily identical with the maximal QRS vector of the spatial vector-cardiogram.

5. Frontal plane QRS axis: "Normal" = 0° to +110°, "left" = 0° to −89°, "right" = +111° through 180° to −90°, inclusive.

6. QRS duration: Durations equal to or greater than 0.12 second are termed abnormal.

Results

Electrocardiograms

1. *Autopsy Series.* The proposed criteria correctly diagnosed 24 of the 32 autopsied cases with right ventricular hypertrophy (table 1). Six of the 24 cases correctly diagnosed by our criteria would have been missed by the criteria of Myers, Klein, and Stofer[1] or Sokolow and Lyon.[2] Seven of the 8 cases missed by our criteria would also have been missed by theirs. The remaining case had an $R-V_1$ greater than 0.7 mv. and an R/S ratio of 0.3, and would therefore have been diagnosed correctly by the criteria of Sokolow[2]; this same finding, however, is present in many normal persons.

2. *Heart Station Series.* Results are sum-

marized in table 2. None of the 29 patients whose electrocardiograms fulfilled the proposed criteria was found to have a normal cardiovascular system: 26 had disorders that characteristically produce right ventricular hypertrophy; 3 had coronary artery disease.

TABLE 1.—*Results of Proposed Criteria for Diagnosis of Right Ventricular Hypertrophy, in Thirty-two Autopsied Cases*

Etiologic diagnosis	Congenital	Chronic cor pulmonale	Rheumatic heart disease	Total
Correctly diagnosed as right ventricular hypertrophy:				
met axis criteria only	0	3	3	6
met V_1 criteria only	0	2	2	4
met both criteria	6	3	5	14
Total	6	8	10	24
Not diagnosed by proposed criteria	0	4	4	8
Total	6	12	14	32

Of the 17 patients with complete RBBB, 1 subject had no heart disease, 15 had coronary disease (3 with previous myocardial infarction), and 1 patient had right ventricular hypertrophy with congenital heart disease (atrial septal defect).

Significance of QRS Duration. The electrocardiographic pattern of complete RBBB was much more frequently due to coronary disease than to right ventricular hypertrophy (table 2). QRS durations of 0.15 second or more were seen only in patients with coronary disease, but this was of little diagnostic help, since the range of QRS durations was wide, the average in the coronary cases being 0.129 second, and QRS duration 0.130 second in the 1 case of right ventricular hypertrophy in the Heart Station series.

Most of the cases that had QRS duration less than 0.120 second and satisfied our criteria had clinical signs of right ventricular hypertrophy (26 of 29 cases, or 90 per cent).

The incidence of "high normal" QRS durations (0.10 to 0.12 second), was about the same

TABLE 2.—*Electrocardiographic Data*

Patient series and diagnosis*	Total number of patients	QRS duration <0.120												QRS duration ≧ 0.120					
		Number of patients	QRS duration		Mean frontal QRS axis†				$R'-V_1$ present	V_1 criteria for RVH			Number of pts	Mean frontal QRS axis				$R'-V_1$ present
			<0.100	≧0.100	Left	Normal	Right +	Right −		R/S > 1	R ≧ 0.5 mv.	Both		Left	Normal	Right +	Right −	
Heart Station:																			
Normal	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	1
Coronary	18	3	2	1	0	2	0	1	1	18	18	18	15	2	10	1	2	10
RVH	27	26	22	4	1	9	13	3	11	22	15	15	1	0	0	0	1	1
Total	46	29	24	5	1	11	13	4	12	40	33	33	17	2	11	1	3	12
Autopsy:																			
Congenital	6	6	5	1	0	0	6	0	1	0	0	0	0	—	—	—	—	—
Cor pulm	12	12	10	2	0	6	6	0	3	9	9	9	0	—	—	—	—	—
RHD	14	13	11	2	0	5	8	0	2	11	10	10	1	0	0	1	0	1
Total	32	31	26	5	0	11	20	0	6	20	19	19	1	0	0	1	0	1
Normal series	103	103	84	19	0	103	0	0	4	7	8	0	—	—	—	—	—	—

* In this and subsequent tables RVH = right ventricular hypertrophy; Congenital = congenital heart disease; Cor pulm. = chronic cor pulmonale; RHD = rheumatic heart disease.

† The limits used for normal, left, and right axis are given in the text under "Definitions." "Right +" = +111° to 180°, and "Right −" = −90° to −179° inclusive.

in the cases of right ventricular hypertrophy (4 of 26 patients, or 15 per cent) as in the normal series (19 of 103, or 18 per cent).

Significance of R or R′ Amplitude. The amplitudes of the latest positive deflection in V_1 were not significantly different in the cases of coronary disease, right ventricular hypertrophy, and the normal case, regardless of QRS duration (table 4). The largest positive deflection found in V_1, however, was a 5.5 mv. R′ in a case of pure pulmonic stenosis.

Significance of Mean QRS Axis. The frontal plane mean QRS axis varied widely, although the highest incidence of right axis deviation was found in the cases of right ventricular hypertrophy, as expected. In 10 of the 29 cases with QRS duration less than 0.12 second, right axis deviation was present but V_1 did not satisfy the proposed criteria.

When the QRS duration was greater than 0.12 second, right axis deviation appeared in 3 of the 15 cases with coronary disease, as well as in the 1 case with right ventricular hypertrophy. The axis was normal in the 1 normal subject in this group of complete RBBB, but was also normal in 10 of the 15 coronary cases.

Significance of $R'-V_1$. A recognizable R′ (0.1 mv. or larger) was found in 4 of the 103 normal subjects, and had an amplitude of less than 0.3 mv. in each case. In the Heart Station series, with QRS duration less than 0.12 second, an $R'-V_1$ was found in cases of coronary disease and cases of right ventricular hypertrophy, with about the same incidence: 1 out of 3 coronary cases, 11 of 26 right ventricular hypertrophy cases. In the autopsy series, an $R'-V_1$ was present in 6 of 31 cases with QRS duration less than 0.12 second.

An initial $Q-V_1$ was present in 4 of the 14 coronary cases with QRS duration of 0.12 second or more, but not in the normal case or the right ventricular hypertrophy case.

TABLE 3.—*Relation between QRS Duration and Presence of $R' - V_1$, for QRS Duration Less than 0.12 Second (Heart Station Series)*

QRS duration (second)	$R' - V_1$		Total
	Absent	Present	
<0.100	16	8	24
≧0.100	1	4	5
Total	17	12	29

TABLE 4.—*Relation between Amplitude of Largest Positive Deflection in V_1 (R or R′) and Etiologic Diagnosis (Heart Station Series)*

Etiologic diagnosis	Total number of cases	QRS duration < 0.120		QRS duration ≧ 0.120	
		Number of cases	Range (mv.)	Number of cases	Range (mv.)
Normal	1	0	—	1	0.55
Coronary	18	3	0.40 to 2.58	15	0.25 to 3.66
RVH	27	26	0.56 to 3.02	1	0.70 to 5.50
Total	46	29	—	17	—

TABLE 5.—*Data from Vectorcardiographic Series of Fifty-seven Patients with a Tall or Late R in Electrocardiographic Lead V_1*

QRS duration (sec)	$R' - V_1$	Etiologic diagnosis	Total number	QRS rotation in transverse projection			Abnormal 10-msec. QRS vector	Terminal slowing
				Counter-clockwise	Figure-eight	Clockwise		
<0.12	Absent	Coronary	2	2	0	0	1	0
		RVH	11	1	4	6	5	0
<0.12	Present	Normal	4	4	0	0	0	0
		Coronary	1	0	1	0	0	0
		RVH	15	5	6	4	5	5
≧0.12	Present	Normal	1	1	0	0	0	1
		Coronary	20	6	11	3	9	20
		RVH	3	1	2	0	2	2
Total			57					

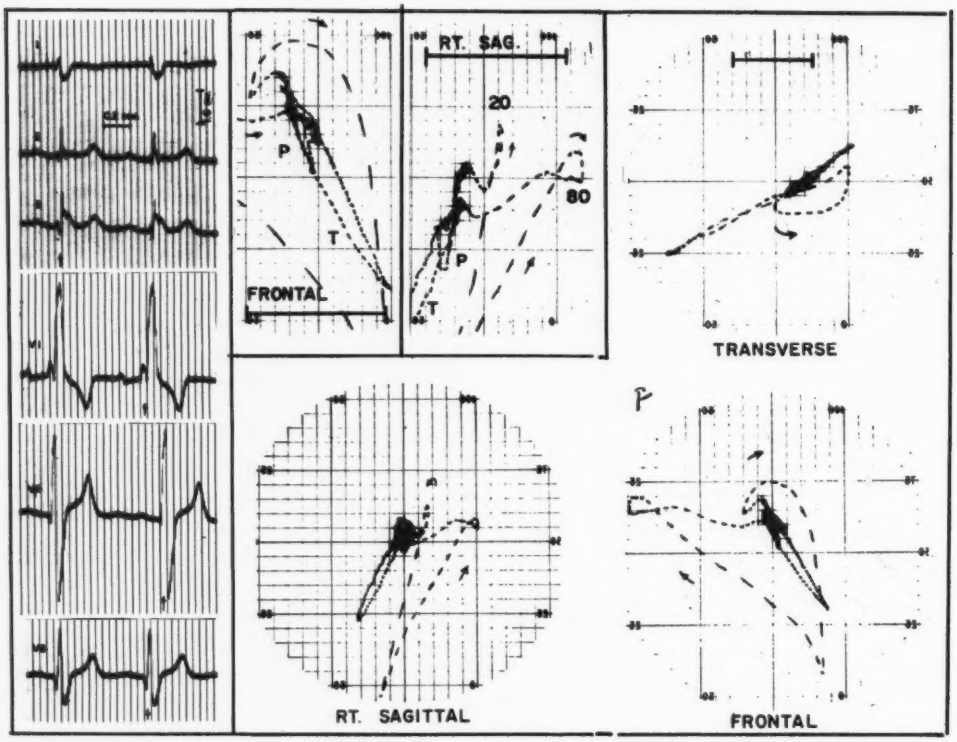

FIG. 1. "Complete right bundle-branch block" in a 28-year-old man with an atrial septal defect (ostium secundum), later confirmed at operation. Pulmonary artery pressure was 90/38 mm. Hg. In the electrocardiogram the arrows indicate simultaneous points in time in different leads. In this and subsequent figures, the vertical reference bar in the electrocardiogram represents 1.0 mv. and the horizontal bar indicates 0.20 second. In the vectorcardiogram horizontal bars = 0.5 mv. The bar given in the upper right transverse view applies to the lower right frontal view, and the lower center sagittal view. Separate standardization bars are shown for the more highly amplified portions in the center panel. Timing is provided by interrupting the cathode-ray beam every 2.5 milliseconds.

The QRS duration is 0.12 second. The R′ in V_1 is of large amplitude, but no larger than that seen in some cases of coronary disease alone (see table 4). The early portion of the QRS complex is normal, but the latter portion is bent anteriorly and to the right, with terminal slowing.

As this case illustrates, marked right ventricular hypertrophy is not always accompanied by clockwise QRS rotation in the transverse projection.

Vectorcardiograms

QRS sÊ Loop Rotation in Transverse View. Results are summarized in table 5. Of 11 patients with clinical and electrocardiographic signs of right ventricular hypertrophy, but no $R'-V_1$, 10 showed an abnormal QRS rotation in the transverse projection (6 clockwise, 4 figure eight), while 1 had a very narrow loop with counterclockwise rotation. Two coronary cases with the same electrocardiographic characteristics had normal counterclockwise QRS rotation in the transverse plane.

Vectorcardiograms were available on 20 patients with an $R' - V_1$ and QRS duration less than 0.12 second. In 4 normal subjects QRS rotation was counterclockwise. In 1 coronary case it was figure eight. In 15 right ventricular hypertrophy cases the 3 types of rotation were about equally represented.

In 24 cases with the electrocardiographic

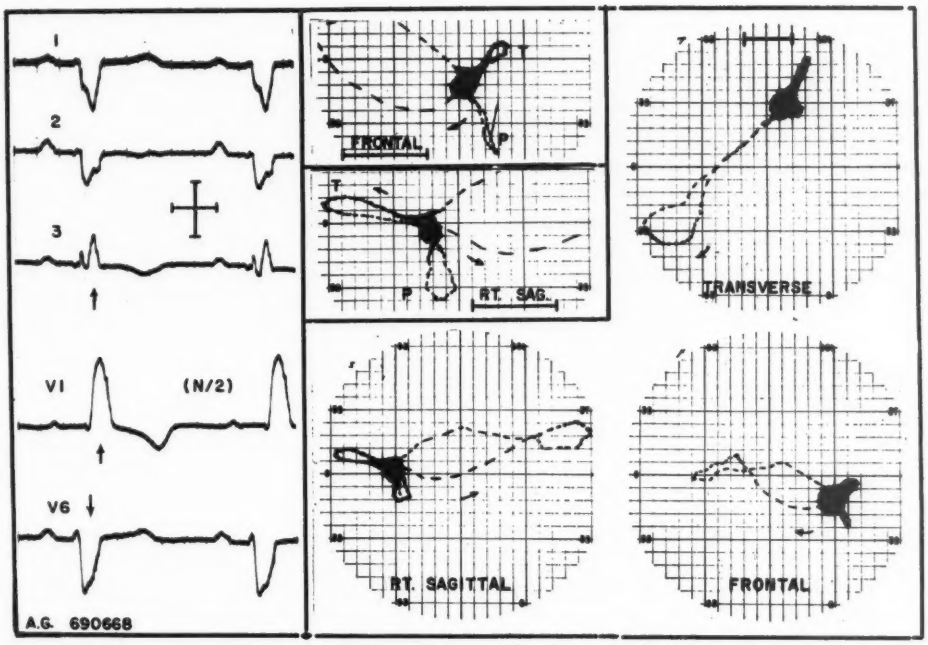

FIG. 2. Electrocardiograms and vectorcardiograms from a 26-year-old man with congenital isolated pulmonic stenosis. Right ventricular pressure was 246/17 mm. Hg on cardiac catheterization. Diagnosis was confirmed at operation.

QRS duration is 0.125 second. The QRS sÊ-loop is displaced anteriorly and to the right. In all projections there is a prominent slowing in the midportion of the loop, rather than the terminal portion. The initial QRS vectors are within normal limits.

pattern of complete RBBB, the 1 normal subject showed normal counterclockwise transverse rotation, 2 of the cases with clinical right ventricular hypertrophy showed figure eight rotation, and 1 counterclockwise (fig. 1), and the coronary cases varied.

Cases with an rsR′S′ in V_1 were not significantly different vectorcardiographically from those with an rsR′. All 4 cases in the vectorcardiographic series were cases of right ventricular hypertrophy, however, and none of the cases with prolonged QRS duration showed an S′.

Abnormal Slowing in QRS sÊ-Loop. All but 1 of the cases with QRS duration of 0.12 second or more showed a marked slowing of the terminal portion of the loop. The 1 exception, shown in figure 2, had a marked slowing in the midportion only. Two coronary cases showed a generalized slowing throughout the whole QRS complex, and 1 had abnormal slowing in the early portion of the loop.

The terminal slow portion of the loop was directed anteriorly and rightward in all cases, and was usually near the transverse plane.

When the QRS duration was less than 0.12 second, accentuated terminal slowing was seen in a few instances, but in most cases there was no more than the normal degree of slowing in the final 20 milliseconds, regardless of the diagnosis, or the presence or absence of an $R'-V_1$.

Initial QRS Vectors. The spatial axis of the 10-millisecond QRS vector was normal in about half of the 57 cases in table 5. In the frontal projection the normal range for this vector is quite wide (0° to −170°, and 0° to +175°),[3] and all 57 cases were within this normal range. In the sagittal projection, 10 coronary and 12 cases of right ventricular hypertrophy had abnormal 10-millisecond vectors.

QRS Plane.[3] In the cases with complete RBBB, the QRS plane was displaced with little or no bending in 2 cases, bent longitudinally along its major axis in 9 cases, and more complexly distorted in 13 cases. No clear correlation between clinical diagnosis and the abnormality of the QRS plane was apparent.

Discussion

Criteria for the Electrocardiographic Diagnosis of Right Ventricular Hypertrophy

The most widely used criteria for the electrocardiographic diagnosis of right ventricular hypertrophy at present are those presented by Myers, Klein, and Stofer,[1] and by Sokolow and Lyon.[2] These investigators clearly demonstrated the potential value of electrocardiography in the diagnosis of right ventricular hypertrophy, but the criteria they suggest are not entirely satisfactory for several reasons: (1) they lead to misdiagnosis in a significant proportion of normal persons; (2) emphasis on lead V_R rather than mean QRS axis results in failure to diagnose some cases with right ventricular hypertrophy; (3) a number of superfluous criteria are included, for example the timing of the "intrinsicoid deflection;" (4) they do not provide for the diagnosis of right ventricular hypertrophy when an R′ appears in V_1.

1. First, as Braunwald, Donoso, Sapin, and Grishman[7] have pointed out, the standards of Sokolow and Lyon are so broad that they would incorrectly attribute right ventricular hypertrophy to a number of normal persons. This is to some extent inevitable whenever rigid diagnostic criteria are set up, necessitating a clear understanding of the difference between a normal heart and a heart with a normal electrocardiogram. The specific criteria of Sokolow and Lyon, however, would have led one to suspect right ventricular hypertrophy in at least 14 per cent of our normal subjects, since 7 of them had an $R-V_1$ taller than 0.7 mv., and 7 others had an R/S ratio in V_1 greater than 1.0.

This difficulty can be resolved at least partially by considering both absolute amplitude of the R wave *and* R/S ratio in the right precordial leads, specifically V_1. An RV_1 larger than 0.5 mv. is not in itself abnormal, and was found in 8 of our 103 normal subjects, but always with a large S wave, so that the R/S ratio was less than 1.0. An R/S ratio greater than 1.0 is similarly not abnormal per se, and was found in 7 of our 103 normal subjects, but always with a small total QRS amplitude such that the R was less than 0.5 mv. The combination of these 2 characteristics was not found in any normal subject in the cases here reported. As with all criteria, it is to be expected that exceptions will appear, but they should be less frequent than with criteria based on amplitude or R/S ratio alone.

The limit of 0.5 mv. for R or $R'V_1$ combined with an R/S ratio of 1.0, which we propose, applies to adult patients, and the specific limits in younger age groups remain to be established. We have not studied patients younger than 10 years of age, but the measurements reported by Ziegler[8] indicate that our criteria probably apply after the age of 5 years. Unfortunately, most electrocardiographic studies of normal subjects report average R wave amplitudes and R/S ratios, with range and standard deviations, but do not evaluate the relation between these 2 measurements in each individual.

2. The second disadvantage of the criteria given by Myers[1] and by Sokolow,[2] in our opinion, lies in their dependence on QRS contour in the unipolar extremity leads, particularly V_R, and their exclusion of mean QRS axis as a diagnostic sign.

Reluctance to use axis deviation as an indication of ventricular hypertrophy can be traced to several sources. First, the arbitrary normal limit of +90°, which was used in early electrocardiography, soon proved to be invalid, since axes between +90° and +110° occur in a significant proportion of normal subjects. Axes in this range do not lead to a dominant R in V_R, and this, together with the concept of "electric position of the heart," led to the conclusion that V_R was a more trustworthy guide than the mean electric axis.

The work of Ashman[9, 10] on the ventricular gradient gave support to this idea by implying that the normal $\hat{A}$ QRS had an extremely wide range. He reported the normal average $\hat{A}$

QRS as +41.7° with a standard deviation of 21.6°, so that the mean ±3 S.D. gave a range of −53° to +136°.[9] In this instance, the use of the standard deviation of a series of observations to define the normal range is misleading, since the distribution around the mean is skewed rather than symmetric. Moreover, in Ashman and Byer's original paper on the gradient,[10] they pointed out that their normal subjects were not a random sample, since some were selected because of their extreme axis measurements, and that at least 1 of the marked right axes plotted in their charts was present only with the patient standing.

In our study and in many reports in the literature it is apparent that only a very small proportion of normal subjects have mean frontal plane QRS axes more positive than +110°.

In our normal series no subject had a mean QRS axis further rightward than +95°. In a series of 200 normal medical students, nurses, and hospital personnel reported by Shipley and Hallaran[11] from Western Reserve University, the most extreme rightward axis observed was +96°, and only 3 cases had an axis of +90° or more. In Ziegler's data,[8] only 1 child in 356 between the ages of 1 and 16 years had a positive axis greater than +105°. Packard, Graettinger, and Graybiel,[12] in their follow-up studies on a large group of normal young aviators, found that 2 of 631 had a QRS axis from +105° to +120° on their original examination in 1940, while none of the 631 (including the original 2) had an axis beyond +90° when re-examined 10 years later. Vastesaeger and Rochet[13] measured the maximal QRS vector of the frontal plane QRS sÊ-loop, (which usually approximates, but is not identical with, the mean frontal plane QRS axis) in 100 normal subjects aged 20 to 45 years, using the Wilson tetrahedron, and found a range of −30° to +110°. Winsor[14] gave the normal range of mean QRS axis as −30° to +102° in 79 normal subjects.

It seems reasonable to conclude from these data that less than 0.15 per cent of the normal adult population will have a mean frontal plane QRS axis more positive than +110°.

Myers and co-workers[1] stated that right axis deviation due to vertical position of the heart can be distinguished from that due to right ventricular hypertrophy by the unipolar extremity leads. We know of no evidence to support this statement. The example given in their figure 1[1] shows a QRS axis very close to +90°, and could be diagnosed as within normal limits without reference to aV_R.

Unipolar extremity leads (V_R, V_L, V_F) are related to mean QRS axis in the same way as the standard extremity leads. A QRS axis from +120° to ±180°, or −60° to −179° will of necessity produce a prominent R in V_R. With the usual QRS sÊ-loop, the ratio of R/Q or R/S in V_R will usually not reach the value of 4.0 or greater suggested by Myers[1] unless the mean QRS axis is between +135° and 180°, or −75° to −179°. Some cases with right axis deviation well beyond normal limits will therefore not show the diagnostic changes in V_R described by Myers.[1] Figure 3 illustrates 1 such case, and 4 similar cases were found in our autopsy series.

It has been suggested that additional right chest leads may show signs of right ventricular hypertrophy when they are absent in lead V_R or V_1. When the QRS axis is displaced toward the right, with relatively little displacement anteriorly, there may be an increase in the R wave in V_{3R} to V_{6R} without diagnostic changes in V_1. In such cases the right axis deviation in the standard leads is almost always diagnostic without reference to V_{3R}, as in Myers,[1] figure 7*A* and *B*.

Leads V_{5R} and V_{6R} are rarely of any additional help, since they largely reflect the frontal plane QRS axis, as evidenced by the fact that they closely resemble either lead III or an inverted lead V_L.

A significant proportion of cases with right ventricular hypertrophy (6 of 32 cases in our autopsy series) show right axis deviation beyond +110°, without diagnostic changes in V_1. We have therefore included right axis deviation as evidence of right ventricular hypertrophy, whether or not V_1 is abnormal. Obviously this criterion will not apply in the presence of dextrocardia.

Ventricular hypertrophy can, of course, be present without either right axis deviation or

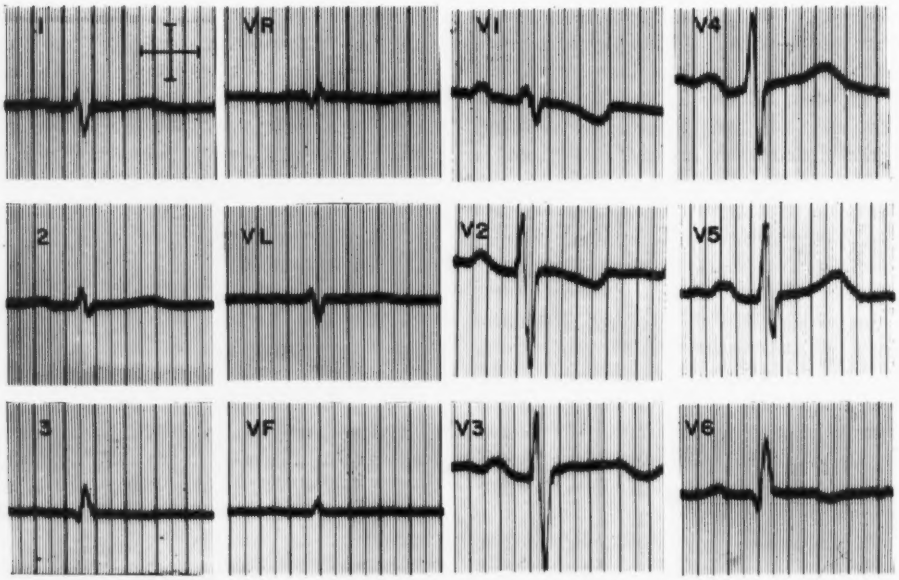

FIG. 3. Electrocardiogram from a 36-year-old woman with chronic cor pulmonale due to pulmonary sarcoidosis. Respiratory tests showed impaired pulmonary function. Roentgenogram showed right ventricular enlargement, and the second pulmonic sound was strongly accentuated.

The limb leads show definite right axis deviation (mean QRS axis = +150°, see text), while V_R and V_1 are within normal limits. QRS duration = 0.07 second. This record shows right ventricular hypertrophy by our criteria but not according to the criteria of Sokolow and Lyon[2] or Myers and associates.[1]

abnormalities in V_1, but we can arrive at no further criteria at present that will identify these cases without at the same time increasing the number of "false positives."

3. A third objection to the previously available criteria for electrocardiographic diagnosis of right ventricular hypertrophy arises from their multiplicity and complexity.

There would be no disadvantage in using a large number of criteria if diagnostic accuracy were improved thereby, but it appears that many criteria, particularly those involving T waves and intrinsicoid deflections, add to the electrocardiographer's burdens without increasing his diagnostic ability.

Inversion of $T-V_1$ is often cited as an indication of right ventricular hypertrophy, or at least as supporting evidence, but it is a frequent normal finding. Of our normal subjects 29 per cent (30 of 103) had an inverted $T-V_1$. Four of these subjects had an $R-V_1$ of 0.5 mv. or more, and therefore met one of Sokolow's criteria for right ventricular hypertrophy. Ziegler's tables[8] report an inverted TV_1 in 86 per cent of a group of 87 normal children between the ages of 5 and 12 years.

The incidence of inverted TV_1 does decrease with age in normal subjects: it was present in 37 per cent of our normal subjects under 30 years of age (27/73), and in only 10 per cent (3/30) of those 30 years and older. In the older age groups, however, an inverted TV_1 is as likely to be due to coronary disease as to right ventricular hypertrophy. In the absence of other abnormalities, therefore, an inverted TV_1 cannot be regarded as evidence of right ventricular hypertrophy at any age.

Ventricular hypertrophy is, of course, often associated with abnormal T waves and S–T segments, which led early observers to introduce the term "strain" to describe these changes. The abnormalities consist of deviation of the S–T segment and T wave in a direction away from the hypertrophied ventricle, until

in extreme cases they point in a direction diametrically opposite the spatial QRS axis. These changes are not specific diagnostically, since coronary disease and its effects on the myocardium, as well as many other abnormalities, can produce this same ST−T alteration.

The "Intrinsicoid Deflection." Measurements of the "intrinsicoid deflection" are not included in this study, or in our clinical interpretation of electrocardiograms, because we believe they are misleading in theory and of no value in practice. Since this opinion is at variance with some textbooks of electrocardiography, the reasons for our views on this subject will be given in some detail.

The normal adult range (mean ± 2 S.D.) for the "intrinsicoid deflection" is given as 0.0044 to 0.030 second for V_1, and 0.0244 to 0.0496 second for V_6 (Kossmann[15]). In our normal subjects the range was 0.000 to 0.030 (mean = 0.017) second for V_1, and 0.020 to 0.050 (mean = 0.038) for V_6.

These are said to represent the time of arrival of the excitation wave in the myocardium "beneath" the precordial electrode. Careful measurements on the exposed mammalian heart, from Lewis and Rothschild[16] to Scher and Young,[17] however, show that activation of the various parts of the right ventricle extends through the last 75 per cent of the total ventricular activation period, or QRS duration. It follows that a large proportion of the normal right ventricle is activated considerably later than the "intrinsicoid deflection" in lead V_1, and that the time of $R-V_1$, if it can be given any localized significance, is at best a reflection of arrival of excitation over an unidentified midportion of the right ventricle.

It seems more likely that no precise meaning referable to a localized area of the myocardium can be assigned to the "intrinsicoid deflection," especially in the diseased heart. As Wilson pointed out, the essential difference between the "intrinsic deflection" of direct contiguous bipolar electrodes, and the "intrinsicoid" deflection of unipolar chest leads, is that *all* parts of the myocardium contribute, though in unequal degree, to a unipolar chest lead. Vectorcardiographic work by Duchosal and Sulzer[18] and in our laboratory[5] supports the conclusion that the R peak in V_1 simply represents the time at which the net sum of the contributions from both ventricles to the electric potential at V_1 reaches a positive maximum, and begins to decrease. The proximity of V_1 to the right ventricle gives right ventricular potentials a slightly greater influence than those from the left ventricle, but the magnitude of this difference is so small that it scarcely affects the QRS contour in V_1.[5]

It is true that many cases with right ventricular hypertrophy have an $R-V_1$ *later* than normal, but only if the R is taller than normal, or if an R′ is present. In both situations, if the QRS duration is normal, the evidence is consistent with the concept that the tall $R-V_1$ of right ventricular hypertrophy represents right ventricular activity that is entirely normal in time, but increased in magnitude. The right ventricular R wave then rises out of the depths of the S wave, and may incorporate the initial small r *en route*, or maintain a separate existence to produce an rsR′.

When the QRS duration is prolonged, or "high normal," on the other hand, conduction delay must be involved, as discussed below and elsewhere.[19]

No case in this report showed a delayed $R-V_1$ in the absence of other QRS abnormalities. If it could be shown empirically that criteria for delayed "intrinsicoid deflection" in V_1 would make possible the diagnosis of right ventricular hypertrophy when other electrocardiographic signs were lacking, then these criteria would clearly have a place in clinical interpretation. Until such evidence is forthcoming, measurement of the "intrinsicoid deflection" seems an unnecessary labor, and might profitably be abandoned.

One example may be given of the contradictions involved in the use of the intrinsicoid deflection. In following some cases as they develop right ventricular hypertrophy, $R-V_1$ is found to increase gradually in size and become later in time, while the R/S ratio in V_6 simultaneously decreases and $R-V_6$ becomes *earlier* in time, the QRS duration remaining unchanged. If the late $R-V_1$ is to be attributed to delayed activation of the right

ventricle, then one must also assume that the left ventricle is being activated *earlier* than usual, which seems improbable.

Reversed Precordial Transition. The normal precordial "transition," with the R/S ratio increasing from V_1 to V_6, is often reversed in right ventricular hypertrophy, but we have not included this in our criteria because it may be obscured when both ventricles are hypertrophied. Our present criteria for left ventricular hypertrophy are an RV_6 greater than 2.5 mv., SV_1 greater than 3.0 mv., or R greater than 2.2 mv. in either lead I or lead II; any one is regarded as evidence of left ventricular hypertrophy. An electrocardiogram that satisfies the criteria for both left and right ventricular hypertrophy is regarded as evidence of combined hypertrophy.

4. A fourth objection to current criteria is that an R′ in V_1 is regarded as evidence of a conduction delay, which makes it impossible to identify right ventricular hypertrophy. This subject is further discussed below and elsewhere.[19] Our criteria apply to the *greatest* positive deflection in V_1, whether an R or R′.

Vectorcardiograms

Right Ventricular Hypertrophy. Our vectorcardiographic investigations in this field were undertaken in the hope that the spatial vectorcardiogram might improve our ability to recognize right ventricular hypertrophy and might clarify the relation between hypertrophy and bundle-branch block. Neither of these aims has been realized to date. The vectorcardiogram has proved to be a great conceptual aid in under-

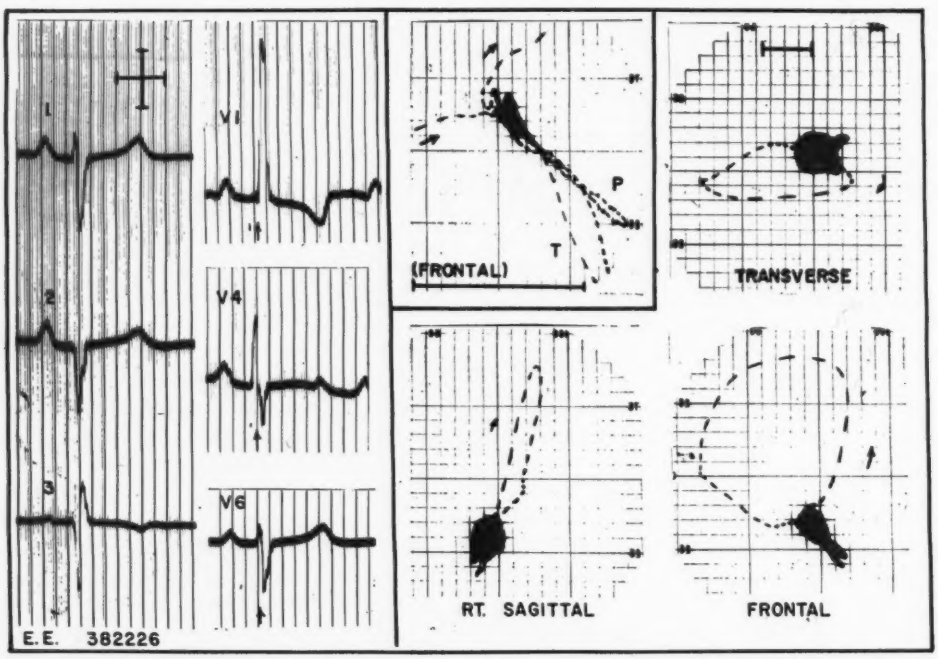

FIG. 4. Electrocardiogram and vectorcardiogram of an 11-year-old girl with tetralogy of Fallot, later confirmed at operation.

In the electrocardiographic precordial leads arrows indicate time of R peak in lead I. QRS duration 0.08 second. The QRS sÊ-loop is displaced toward the right shoulder and anteriorly.

These records illustrate extreme effects of right ventricular hypertrophy. On comparison with the records in figure 7, which show a similar QRS axis in a patient with coronary disease, the only significant differences are the total QRS duration, and the slight terminal slowing of the QRS sÊ-loop in figure 7.

standing the widely varying patterns seen in different scalar leads, but in our hands it has not been of much additional help in the differential diagnosis of right ventricular hypertrophy.

The characteristic alterations of the QRS sÊ-loop with right ventricular hypertrophy can be summarized as follows: the early QRS vectors take an abnormal direction, often simulating the changes of old myocardial infarction; the midportion of the loop, usually including the maximal QRS vector, is displaced rightward and anteriorly, the degree of this displacement being roughly proportional to the degree of right ventricular hypertrophy; the terminal portion of the loop may be normal in direction, or may be directed more anteriorly than normal. Evidence cited below suggests that the anteriorly directed terminal segments may indicate conduction delay even when no slowing is apparent.

Rightward and anterior displacement of the midportion of the loop can produce clockwise rotation of the QRS sÊ-loop in the transverse projection, as described by Grishman and his collaborators[20, 21] and others (fig. 4). With varying degrees of displacement of the QRS sÊ-loop, however, the transverse projection may show a figure-eight, or a normal counterclockwise QRS rotation, as indicated by the summary in table 5, and figures 5 and 6. Moreover, clockwise or figure-eight QRS rotation in this projection is not pathognomonic of right ventricular hypertrophy, since it also occurs frequently with myocardial infarction or arteriosclerotic heart disease, particularly when the QRS duration is 0.12 second or more (fig. 7). With these reservations our data justify at least 2 conclusions: (1) in normal persons the

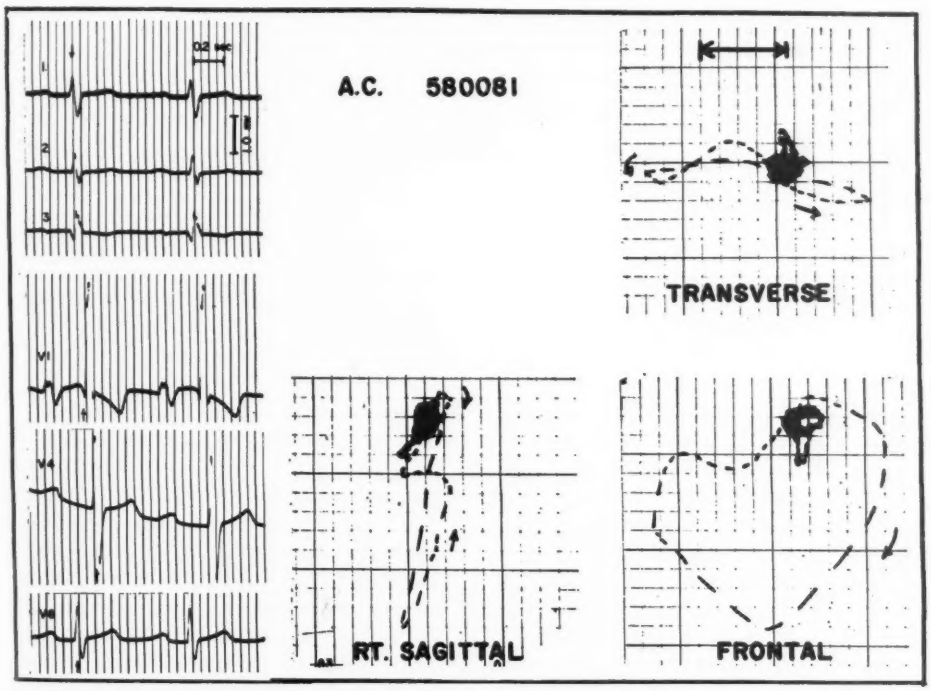

FIG. 5. Electrocardiogram and vectorcardiogram from a 35-year-old man with severe rheumatic mitral stenosis, and right ventricular hypertrophy, confirmed at autopsy. The electrocardiogram shows normal axis, with very tall R — V_1, and very large R/S — V_1 ratio. QRS duration 0.09 second. QRS sÊ-loop is almost linear in the transverse projection.

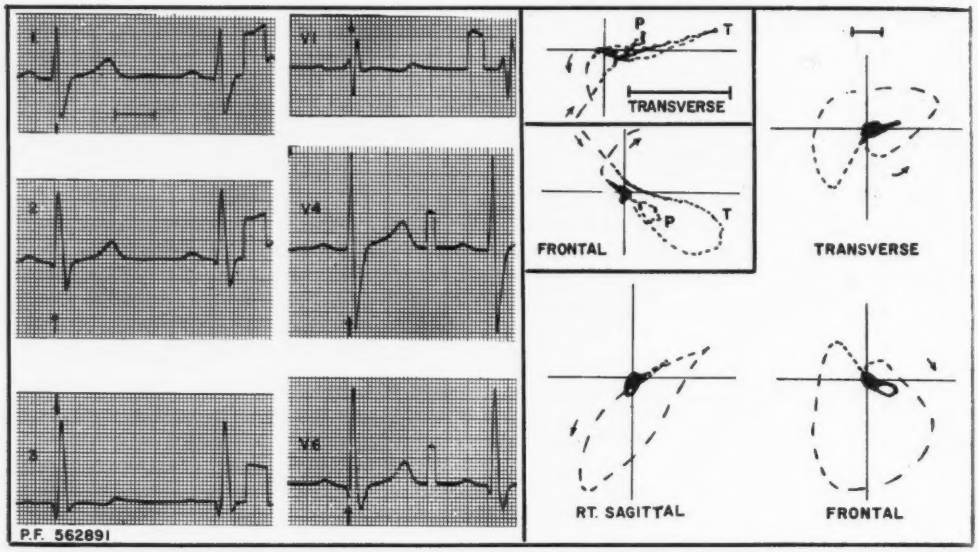

FIG. 6. Electrocardiogram and vectorcardiogram from an 18-year-old man with the Eisenmenger complex.

QRS duration is 0.10 second, with the electrocardiographic configuration that has been termed "incomplete right bundle-branch block." QRS axis is within normal limits. Since the $R' - V_1$ is 0.7 mv. and the R'/S ratio in V_1 is 1.1, this electrocardiogram meets our criteria for the diagnosis of right ventricular hypertrophy.

In the vectorcardiogram, the only abnormality appears in the right sagittal view, where the QRS sÊ-loop, after starting in a normal direction, turns and runs posteriorly. The centripetal limb of the loop lies relatively anteriorly, so that the right sagittal QRS rotation is broadly counterclockwise, a definitely abnormal finding.

QRS sÊ-loop rotation in the transverse view is always counterclockwise, even when an $R'-V_1$ is present; (2) clockwise or figure-eight rotation in the transverse projection usually indicates right ventricular hypertrophy, *provided* the QRS duration is less than 0.12 second. In pediatric cardiology, where the question of coronary disease rarely arises, the latter conclusion can be extended to QRS complexes longer than 0.12 second.

Whether the spatial vectorcardiogram will identify some cases of anatomic right ventricular hypertrophy that do not have diagnostic signs in the routine scalar electrocardiogram is a question we cannot answer from the small number of patients in this category we have studied, but in 2 such cases (not included in table 5) the vectorcardiogram was within normal limits.

The Problem of "Bundle-Branch Block." One of the earliest results of the renewal of interest in spatial vectorcardiography in this country in 1949 and 1950 was the discovery that an $RSR'-V_1$ might exist with either of 2 different types of spatial vectorcardiogram. As Lasser, Borun, and Grishman described,[21] an early and a late inflection of the QRS sÊ-loop is directed toward the right chest in both types, but in one the intervening portion of the loop progresses clockwise in the transverse projection, and in the other, counterclockwise. Lasser and co-workers[21] reported that the clockwise type indicated right ventricular hypertrophy, while the counterclockwise type occurred with normal hearts or myocardial disease (presumably infarction), a hypothesis not borne out by our observations (table 5 and figs. 1, 6, 7).

They also concluded that "QRS vector loops of those cases not associated with right ventricular hypertrophy are all characterized by a slow irregular terminal loop directed to the

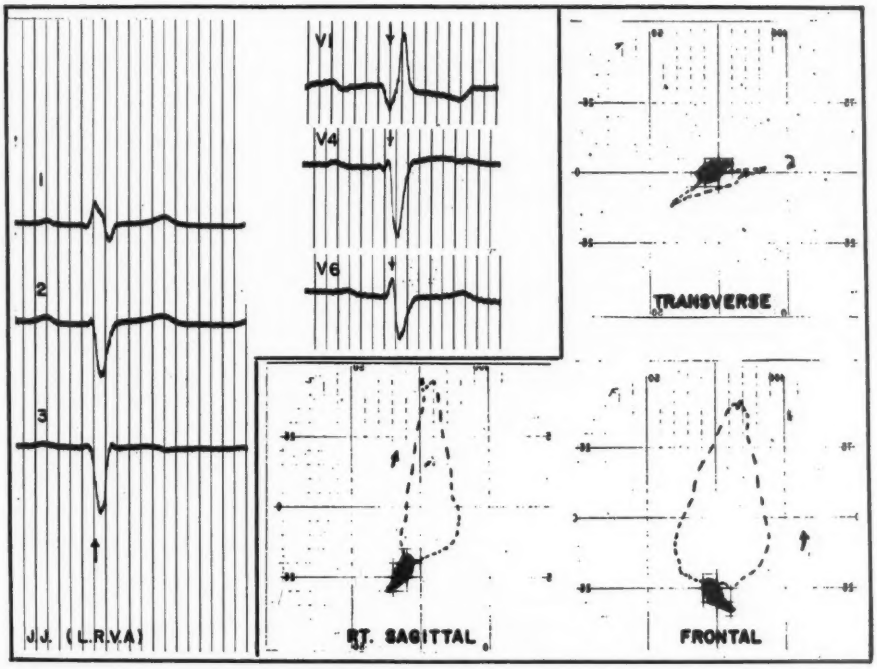

FIG. 7. "Complete right bundle-branch block" in a 60-year-old man, with clinical history and electrocardiographic findings of acute anterior myocardial infarction 2 years prior to this record. QRS duration 0.130 second. The QRS sÊ-loop is displaced vertically upward, and slightly anteriorly, giving a narrow but clockwise QRS loop in the transverse view. As this example shows, the latter finding is not pathognomonic of right ventricular hypertrophy, at least in adults, since it may appear with myocardial infarction.

right and anteriorly. . .,"[21] while we have encountered this same finding in cases of right ventricular hypertrophy (fig. 7). It is probable that their conclusions were influenced by the fact that their 5 cases of right ventricular hypertrophy all had normal QRS duration, while in the 3 nonhypertrophied cases the QRS duration was prolonged.

Grishman's criterion for distinguishing between right ventricular hypertrophy and right bundle-branch block is an abnormal slowing of the terminal portion of the QRS sÊ-loop in the latter.[21] Our observations do not support this conclusion, although we agree that the "benign" right bundle-branch block occasionally seen in *normal subjects* usually has counterclockwise QRS rotation in the transverse projection.

In electrocardiograms that might be interpreted as "incomplete right bundle-branch block," i. e., with QRS duration less than 0.12 second and an rsR′$-V_1$, terminal slowing was rare, and not related to clinical diagnosis (figs. 4–6). In patients with QRS duration of 0.12 second or more, and R′$-V_1$, terminal slowing in the coronary cases was indistinguishable from that in right ventricular hypertrophy (figs. 1, 7, 8).

It should be emphasized that while terminal slowing of the QRS sÊ-loop is the spatial analog of the slurred S$-$1 and R′$-V_1$ of the scalar electrocardiogram, it is not direct evidence of slowed intraventricular conduction. The speed with which the cathode ray spot moves during the QRS complex is a function of the *rate of change* of direction and magnitude of the net vector sum of electric forces produced by ventricular depolarization, and is therefore not necessarily related to the speed with which the depolarization wave travels through any

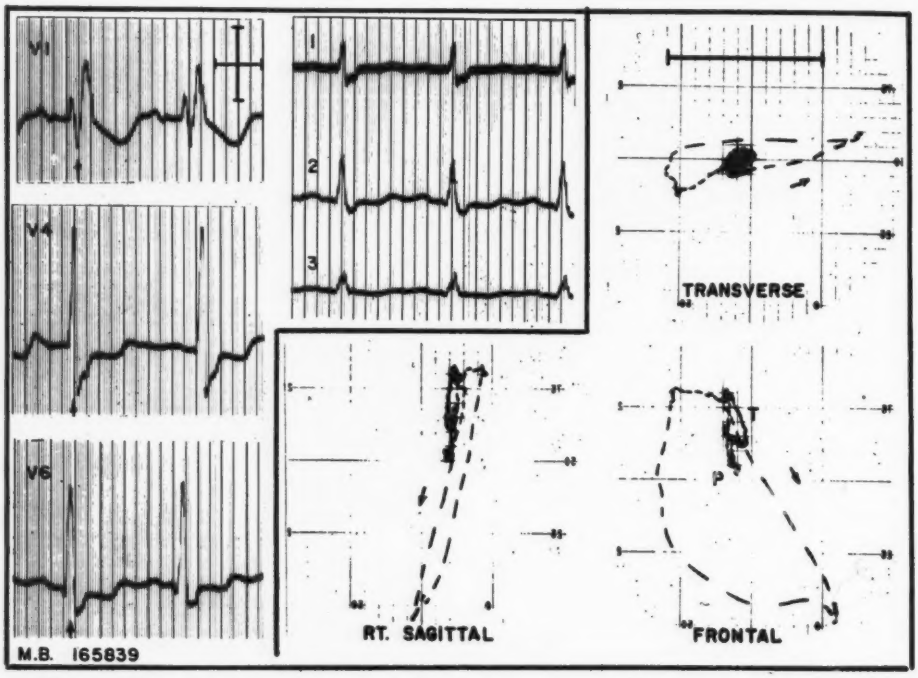

FIG. 8. Electrocardiogram and vectorcardiogram from a 66-year-old woman with right ventricular hypertrophy (not included in table 5). Her principal clinical lesions were bronchiectasis and emphysema, and the right ventricle was enlarged radiologically, but in this age group coronary disease cannot be excluded. The QRS duration is 0.10 second and there is a prominent R′ in V_1, which satisfies the criteria proposed for the diagnosis of right ventricular hypertrophy. The vectorcardiogram shows normal QRS rotation in the transverse view, slight terminal slowing, and abnormal QRS rotation in the right sagittal view. Upward S-T displacement is also prominent in the vectorcardiogram.

particular area of the myocardium. It would be possible, for example, for the spot to remain entirely motionless during a large part of the QRS complex, even though activation were spreading through the myocardium, if the vector *sum* of the advancing activation fronts in all parts of the heart at each instant maintained the same magnitude and direction. In practice, this rarely happens, probably because of the complex structure of the mammalian heart, but it is theoretically possible, and implies that slowing of the spot is theoretically compatible with normally rapid spread of ventricular activation. Conversely, a very slowly advancing activation wave could produce normal or rapid movement of the spot, by changing its *direction* rapidly. *Prolongation* of the total QRS duration, on the other hand, *is* definite evidence of conduction delay, though not of its site.

With our present knowledge, one can only say that when the electrocardiogram shows the pattern designated as "complete right bundle-branch block," the QRS sÊ-loop will almost always show abnormal slowing of some part of the loop. To assert that this slowing is therefore pathognomonic of conduction delay in the bundle branches is to assume facts not in evidence.

Braunwald and associates[22, 23] have taken a direct approach to the question of delayed ventricular activation by measuring the interval between the beginning of electric and of mechanical ventricular activity, by means of cardiac catheterization. Their results complicate the question still further by showing that neither the total QRS duration nor the presence of an $R'-V_1$ is a reliable indication of delayed mechanical activation. They found terminal slowing of the QRS sÊ-loop only in cases with

delayed right ventricular contraction, but their observations did not include studies on normal subjects with QRS duration less than 0.10 second and $R'-V_1$.

Initial QRS Vectors. The normal 10-millisecond QRS vector has a wide range, and may be directed toward right or left, superiorly or inferiorly. It is always anterior, however, and in the right sagittal projection the normal range with our technic is from $-70°$ to $0°$ and $0°$ to $+88°$,[3] thus excluding the extreme superior and inferior segments.

The direction of the initial QRS vectors was normal in about half the cases in table 5.

In general, the 10-millisecond QRS vector was more inferiorly directed in patients with clinical right ventricular hypertrophy than in normal subjects but was no further to the left than normal, contrary to the observations of Fowler and Helm.[24] The most important finding is that cases of right ventricular hypertrophy may have abnormally directed initial vectors simulating myocardial infarction.

Richman and Wolff[25] have reported that initial QRS vectors pointing toward the left, inferiorly, and anteriorly, indicate left BBB. They suggest that this criterion can be used to identify left BBB in cases where the standard leads suggest right BBB, but precordial leads suggest left BBB. Three of the cases in table 5 with QRS duration of 0.12 second or more had 10-millisecond QRS vectors with this orientation, but in each case the standard limb and precordial leads were characteristic of *right* BBB.

The Wolff-Parkinson-White anomaly sometimes produces a tall R wave in V_1, simulating right BBB, and 1 case of this kind (not included in table 5) has been studied in this laboratory. The transverse projection of the QRS loop was displaced so that it lay entirely anteriorly, but was *counterclockwise* in rotation, a unique finding in our vectorcardiographic collection.

Origin of Q, R, or R′ in V_1

It is worth emphasizing that spatial vectorcardiography cannot *explain* the origin of the waves in the scalar electrocardiogram: it simply records them in a different way. Records from electrodes on the body surface can provide grounds for speculation about the specific events in the myocardium which give rise to different parts of the electrocardiogram or the vectorcardiogram, but confirmation requires correlation with direct epicardial or intramyocardial leads. Unfortunately the few published studies using direct leads in man give apparently conflicting results.[26, 27]

The 12 cases in our vectorcardiographic series that showed a Q in V_1 had 10-millisecond QRS vectors directed leftward or posteriorly, most of them outside the normal spatial range. Since an initial R may be absent in V_1 in normal persons, the $Q-V_1$ in our cases is not particularly surprising, but the fact that the initial vectors are so often outside the normal spatial range requires explanation. In the coronary cases (4 out of the 12) this is presumably analogous to the usual Q wave of myocardial infarction, in which loss of some of the normal electric forces alters the resultant vector. In the cases of right ventricular hypertrophy (8 of 12), the resultant vector must be altered by addition of new forces or an increase in electric forces normally present, but why the initial vectors should be displaced in this direction is not clear.

We are unwilling to assume anatomic rotation of the heart around its long axis as an explanation, particularly in view of Grant's[28] evidence that relatively little such rotation occurs. The concept that a unipolar lead that gives a QRS complex with a tall R wave must "face" the left ventricle[29] seems to us untenable, particularly in an abnormal heart.

When the QRS duration is less than 0.12 second it seems probable that the tall R or R′ in V_1 is the result of vectors of increased magnitude from the hypertrophied right ventricle, which is in accord with the results of Carouso, Chevalier, Latsche, and Lenegre,[26] but difficult to reconcile with those of McGregor.[27] The interpretation of unipolar records from the ventricular surface is rendered difficult, however, by the fact that a unipolar electrocardiogram, even from the epicardium, is significantly influenced by the entire heart, and a negative deflection from one point on the right ventricular surface does not exclude the possibility of large positive deflections at other

points, e.g., the pulmonary conus. Why hypertrophied ventricular fibers should produce abnormally large voltages is not known, and one wonders how much of this increased voltage arises from the decreased distance between the enlarged heart and the chest wall. In the cases with coronary disease myocardial scarring may produce the same net result by eliminating part of the normal left ventricular contribution to the QRS sÊ-loop.

As noted above, conduction delay may or may not also be present when the QRS duration is less than 0.12 second.[22] When the QRS duration is 0.12 second or more, it may be assumed that the late R or $R'-V_1$ actually represents delayed right ventricular activation, as Wilson's group[30] originally predicated. In the exceptional cases where a prolonged QRS occurs with right ventricular hypertrophy, the site of the conduction delay may well be in the hypertrophied myocardium itself.

Chronic Cor Pulmonale

All electrocardiographic criteria for the diagnosis of right ventricular hypertrophy, including ours, fail most often in older patients with chronic cor pulmonale, as many of the cases reported by Walker, Helm, and Scott[31, 32] and by Salazar and Sodi-Pallares[33] demonstrate. Such patients often have a mean frontal QRS axis from +80° to +100°, and an R/S ratio in V_6 of 1.0 or less, although V_1 is normal. In patients over the age of 40, these characteristics may be regarded as presumptive evidence of chronic cor pulmonale, although they may occasionally occur with arteriosclerotic heart disease.

Differential Diagnosis of Coronary Disease and Right Ventricular Hypertrophy

Myocardial scarring as a result of circumscribed myocardial infarction or the more diffuse fibrosis produced by chronic coronary insufficiency can lead to electrocardiographic changes in axis and in V_1 identical with those of right ventricular hypertrophy.[34, 35] When definitely abnormal Q waves are present, the diagnosis of old myocardial infarction is suggested, but it is impossible to be sure that right ventricular hypertrophy does not co-exist (fig. 8). In the absence of signs of old myocardial infarction, differential diagnosis from the electrocardiogram or vectorcardiogram is difficult.

Use of Diagnostic Criteria

Any proposal to establish specific criteria for clinical diagnosis should bear a *caveat*. Criteria for electrocardiographic or vectorcardiographic diagnosis, attempting to relate electric phenomena to changes in structure and function of the heart, are unavoidably empiric. Ideal criteria would enable a correct diagnosis in every case and would exclude all normal subjects, but neither of these aims is likely to be completely realized in the study of biologic material.

With the vectorcardiogram, as with the conventional electrocardiogram, a record "outside of normal limits" does not necessarily mean heart disease. Criteria for electrocardiographic or vectorcardiographic diagnosis of right ventricular hypertrophy provide diagnostic clues that should be appropriately weighed with all other available information, and when no other evidence to support the diagnosis is forthcoming, isolated cardiographic findings should in most cases be ignored by the clinician and filed for future reference by the investigator.

Summary and Conclusions

Electrocardiographic and vectorcardiographic studies have been carried out on normal subjects and patients with heart disease with 2 aims, to establish improved criteria for the electrocardiographic diagnosis of right ventricular hypertrophy, and to examine the relation between right ventricular hypertrophy and right bundle-branch block. Data from 238 cases have been analyzed, comprising electrocardiograms from 32 autopsied cases of right ventricular hypertrophy and 46 hospital patients with electrocardiographic signs of right ventricular hypertrophy or "complete right bundle-branch block"; electrocardiograms and vectorcardiograms from 103 normal subjects and 57 patients with a tall or late $R-V_1$.

The following criteria for the electrocardiographic diagnosis of right ventricular hypertro-

phy are proposed: QRS duration less than 0.12 second, plus either a mean frontal plane axis from $+110°$ to $\pm 180°$, or $-91°$ to $\pm 180°$, *or* R/S or R′/S ratio in V_1 greater than 1.0, with R or R′ greater than 0.5 millivolt. The advantages over previously published criteria include fewer misdiagnoses in normal persons, correct diagnosis in a higher proportion of cases of right ventricular hypertrophy, elimination of unnecessary criteria, and applicability to records with $R'-V_1$.

A small proportion of records that meet these criteria will be from patients with coronary artery disease and no right ventricular hypertrophy. This is equally true of other published criteria.

Prolongation of the QRS duration to 0.12 second or more, with the electrocardiographic pattern of the right bundle-branch block, is much more commonly due to coronary disease than to right ventricular hypertrophy. It occasionally occurs in persons without heart disease.

An $R'-V_1$ with normal QRS duration occurs frequently with right ventricular hypertrophy, and occasionally in normal subjects and patients with coronary disease. The designation of this pattern as "incomplete right bundle-branch block" is misleading and should be abandoned until more information is available.

The spatial vectorcardiogram is sometimes helpful in establishing the presence of heart disease in a patient with the electrocardiographic pattern of complete right bundle-branch block, since figure eight or clockwise rotation of the QRS sÊ-loop in the transverse projection has not been observed in normal persons, even with prolonged QRS duration.

In right ventricular hypertrophy, transverse projection QRS rotation is clockwise or figure eight in the majority of cases, but this also occurs with coronary disease and is therefore not pathognomonic. Initial QRS vectors or other characteristics of the QRS sÊ-loop do not help to distinguish the cases of coronary disease.

Terminal slowing of the QRS sÊ-loop occurs in most cases with the electrocardiographic pattern of "complete right bundle-branch block," but at present provides no diagnostic information beyond that available from the QRS contour and duration in the scalar electrocardiogram.

One case of Wolff-Parkinson-White anomaly is described, in which the electrocardiogram imitated right ventricular hypertrophy, but the spatial vectorcardiogram was not characteristic of right ventricular hypertrophy.

Summario in Interlingua

Studios electrocardiographic e vectocardiographic ha essite executate in subjectos normal e in patientes con morbo cardiac con le 2 objectivos (1) de establir meliorate criterios pro le diagnose electrocardiographic de hypertrophia dextero-ventricular e (2) de examinar le relation inter hypertrophia dextero-ventricular e bloco de branca dextere. Esseva analysate datos ab 238 casos, incluse electrocardiogrammas ab 32 necropsiate casos de hypertrophia dextero-ventricular e ab 46 patientes hospitalisate con signos electrocardiographic de hypertrophia dextero-ventricular o de "complete bloco de branca dextere" e electrocardiogrammas e vectocardiogrammas ab 103 casos normal e 57 patientes con alte o retardate $R - V_1$.

Le sequente criterios es proponite pro le diagnose electrocardiographic de hypertrophia dextero-ventricular: Duration de QRS de minus que 0,12 secundas e in plus (a) axe medie de plano frontal inter $+110°$ e $\pm 180°$ o inter $-91°$ e $\pm 180°$ o (b) un proportion R/S o R′/S in V_1 de plus que 1,0, con R o R′ de plus que 0,5 millivolt. Le avantages in comparation con previemente describite criterios include minus diagnoses erronee in subjectos normal, correcte diagnoses in un alte procentage de casos de hypertrophia dextero-ventricular, elimination de criterios non requirite, e applicabilitate a registrationes con $R' - V_1$.

Un parve numero de registrationes que satisface iste criterios va esser trovate inter le registrationes ab patientes con morbo de arteria coronari e sin hypertrophia dextero-ventricular. Isto es equalmente ver pro altere criterios publicate.

Le prolongation del duration de QRS a 0,12 secundas o plus in casos con le configuration

electrocardiographic de bloco de branca dextere es multo plus communmente debite a morbo coronari que a hypertrophia dextero-ventricular. In rar casos illo occurre in subjectos sin morbo cardiac.

Un $R'-V_1$ con duration normal de QRS occurre frequentemente in casos de hypertrophia dextero-ventricular. Illo occurre sporadicamente in subjectos normal e in patientes con morbo coronari. Le uso del termino "incomplete bloco de branca dextere" pro iste configuration es infelice e deberea esser abandonate usque informationes additional deveni disponibile.

Le vectocardiogramma spatial es a vices utile in establir le presentia de morbo cardiac in un patiente qui exhibi le configuration electrocardiographic de complete bloco de branca dextere, proque rotation in forma de '8' o rotation dextrorse del spira sÊ de QRS in le projection transverse ha non essite observate in subjectos normal, mesmo in casos de QRS prolongate.

In hypertrophia dextero-ventricular, le rotation de QRS in le projection transverse es dextrorse o del forma de '8' in le majoritate del casos, sed le mesme observation vale pro morbo coronari, e per consequente illo non es pathognomonic. Vectores de QRS initial o altere characteristicas del spira sÊ de QRS es sin valor in differentiar le casos de morbo coronari.

Relentation terminal del spira sÊ de QRS occurre in le majoritate del casos exhibiente le configuration electrocardiographic de "complete bloco de branca dextere," sed al tempore presente iste phenomeno provide nulle information diagnostic in ultra de lo que es providite per le contorno de QRS e per le duration de illo in le electrocardiogramma scalar.

Es describite un caso del anomalia de Wolff-Parkinson-White in que le electrocardiogramma reflecteva hypertrophia dextero-ventricular durante que le vectocardiogramma spatial non esseva characteristic de iste condition.

Acknowledgment

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REFERENCES

1 Myers, G. B., Klein, H. A., and Stofer, B. E.: The electrocardiographic diagnosis of right ventricular hypertrophy. Am. Heart J. **35:** 1, 1948.

2 Sokolow, M., and Lyon, T. P.: The ventricular complex in right ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am. Heart J. **38:** 273, 1949.

3 Milnor, W. R.: The normal vectorcardiogram and a system for the classification of vectorcardiographic abnormalities. Circulation **16:** 95, 1957.

4 Carter, E., Richter, C. P., and Greene, C. H.: A graphic application of the principle of the equilateral triangle for determining the direction of the electrical axis of the heart in the human electrocardiogram. Bull. Johns Hopkins Hosp. **30:** 162, 1919.

5 Milnor, W. R., Talbot, S. A., and Newman, E. V.: A study of the relationship between unipolar leads and spatial vectorcardiograms, using the panoramic vectorcardiograph. Circulation **7:** 545, 1953.

6 Smith, H. L.: The relation of the weight of the heart to the weight of the body and of the weight of the heart to age. Am. Heart J. **4:** 79, 1928.

7 Braunwald, E., Donoso, E., Sapin, S. O., and Grishman, A.: A study of the electrocardiogram and vectorcardiogram in congenital heart disease. I. Electrocardiographic criteria for ventricular hypertrophy. Am. Heart J. **50:** 591, 1955.

8 Ziegler, R. F.: Electrocardiographic studies in normal infants and children. Springfield, Ill., Charles C Thomas, 1951.

9 Ashman, R.: A statistical study of the ventricular gradient and of the QRS complex of the electrocardiogram. Arch. Inst. cardiol. México **15:** 266, 1945.

10 —, and Byer, E.: The normal human ventricular gradient. I. Factors which affect its direction and its relation to the mean QRS axis. Am. Heart J. **25:** 16, 1943.

11 Shipley, R. A., and Hallaran, W. R.: The 4-lead electrocardiogram in 200 normal men and women. Am. Heart J. **11:** 325, 1936.

12 Packard, J. M., Graettinger, J. S., and Graybiel, A.: Analysis of the electrocardiograms obtained from 1000 young healthy aviators: Ten year follow-up. Circulation **10:** 384, 1954.

13 Vastesaeger, M. M., and Rochet, J.: Les propriétés du vectocardiogramme spatial de l'homme normal. Ses variations physiologiques. Travaux d. Lab. Inst. Solvay de Physiologie, **29:** 55, 1944.

14 Winsor, T. (Ed.): Electrocardiographic Test

Book. New York, American Heart Association, Inc., 1956.

[5] KOSSMANN, C. E.: The normal electrocardiogram. Circulation **8:** 920, 1953.

[6] LEWIS, T., AND ROTHSCHILD, M. A.: The excitatory process in the dog's heart. Part II. The ventricles. Phil. Trans. Roy. Soc. **206:** 181, 1915.

[7] SCHER, A. M., AND YOUNG, A. C.: The pathway of ventricular depolarization in the dog. Circulation Research **4:** 461, 1956.

[8] DUCHOSAL, P. W., AND SULZER, R.: La Vectocardiographie. Basel, S. Karger, 1949.

[9] MILNOR, W. R., AND BERTRAND, C. A.: The electrocardiogram in atrial septal defect. A study of 24 cases, with observations on the RSR′ – V_1 pattern. Am. J. Med. **22:** 223, 1957.

[10] DONOSO, E., SAPIN, S. O., BRAUNWALD, E., AND GRISHMAN, A.: A study of the electrocardiogram in congenital heart disease. II. Vectorcardiographic criteria for ventricular hypertrophy. Am. Heart J. **50:** 674, 1955.

[11] LASSER, R. P., BORUN, E. R., AND GRISHMAN, A.: A vectorcardiographic analysis of the RSR′ complex of the unipolar chest lead electrocardiogram. III. Am. Heart J. **41:** 667, 1951.

[12] BRAUNWALD, E., DONOSO, E., SAPIN, S. O., AND GRISHMAN, A.: Right bundle-branch block. Hemodynamic, vectorcardiographic and electrocardiographic observations. Circulation **13:** 866, 1956.

[13] —, FISHMAN, A. P., AND COURNAND, A.: Time relationship of dynamic events in the cardiac chambers, pulmonary artery, and aorta in man. Circulation Research **4:** 100, 1956.

[14] FOWLER, N. O., AND HELM, R. A.: The spatial QRS loop in right ventricular hypertrophy with special reference to the initial component. Circulation **7:** 573, 1953.

[15] RICHMAN, J. L., AND WOLFF, L.: Left bundle branch block masquerading as right bundle branch block. Am. Heart J. **47:** 383, 1954.

[16] CAROUSO, G. J., CHEVALIER, H. A., LATSCHA, I., AND LENEGRE, J.: Epicardial electrocardiograms recorded in the course of seven cases of heart surgery. Circulation **5:** 48, 1952.

[17] MCGREGOR, M.: The genesis of the electrocardiogram of right ventricular hypertrophy. Brit. Heart J. **12:** 351, 1950.

[18] GRANT, R. P.: The relationship between the anatomic position of the heart and the electrocardiogram. A criticism of "unipolar" electrocardiography. Circulation **7:** 890, 1953.

[19] KOSSMANN, C. E., BERGER, A. R., BRUMLIK, J., AND BRILLER, S. A.: An analysis of causes of right axis deviation based partly on endocardial potentials of the hypertrophied right ventricle. Am. Heart J. **35:** 309, 1948.

[20] WILSON, F. N., MACLEOD, A. G., AND BARKER, P. S.: The order of ventricular excitation in human bundle branch block. Am. Heart J. **7:** 305, 1932.

[21] WALKER, I. C., JR., HELM, R. A., AND SCOTT, R. C.: Right ventricular hypertrophy. I. Correlation of isolated right ventricular hypertrophy at autopsy with the electrocardiographic findings. Circulation **11:** 215, 1955.

[22] —, SCOTT, R. C., AND HELM, R. A.: Right ventricular hypertrophy. II. Correlation of electrocardiographic right ventricular hypertrophy with the anatomic findings. Circulation **11:** 223, 1955.

[23] SALAZAR, M. M., AND SODI-PALLARES, D.: Estudio sobre el Corazon Pulmonar Cronico. Analisis de 14 Casos. Arch. Inst. cardiol. México **16:** 22, 1946.

[24] ELEK, S. R., ALLENSTEIN, B. J., KORNBLUTH, A. W., GRIFFITH, G. C., AND LEVINSON, D. C.: The spatial vectorcardiogram in myocardial infarction typified by prominent R waves in leads aV_R and V_1. Am. Heart J. **47:** 477, 1954.

[25] MYERS, G. B.: QRS-T patterns in multiple precordial leads that may be mistaken for myocardial infarction. II. Right ventricular hypertrophy and dilatation. Circulation **1:** 860, 1950.

But weightier still are the contentment which comes from work well done, the sense of the value of science for its own sake, insatiable curiosity, and, above all, the pleasure of masterly performance and of the chase. These are the effective forces which move the scientist. The first condition for the progress of science is to bring them into play.—L. J. HENDERSON, 1878–1942.

Aneurysmal Dilatation of the Aortic Sinuses in Marfan's Syndrome

Angiocardiographic and Cardiac Catheterization Studies in Identical Twins

By Israel Steinberg, M.D., Joseph L. Mangiardi, M.D., and William J. Noble, M.D.

Aneurysmal dilatation of the aortic sinuses in identical twins, aged 2 years, was disclosed after angiocardiography. Knowledge of the association of aortic sinus aneurysms and Marfan's syndrome led to the discovery of bilateral dislocated lenses; these, plus mildly arched palates, dolichocephaly, and slender fingers established the diagnosis of arachnodactyly. Right heart catheterization proved to be normal. A patent foramen ovale in 1 twin permitted pressure measurements in the left atrium and ventricle. Significant mitral insufficiency and aortic stenosis were excluded by the character of the left atrial and ventricular pressures. Aortic sinus dilatation is due to medial degeneration, a common finding in Marfan's syndrome. Endocardial or subendocardial (myxomatous) involvement of the left ventricle is probably the cause of the left ventricular hypertrophy.

RECENTLY, aneurysmal dilatation of the aortic sinuses in 3 adults with arachnodactyly was demonstrated during life by angiocardiography.[1] Previously such aortic lesions were detected only at necropsy.[2–6] Aneurysmal dilatation of the aortic sinuses in identical twins, aged 2 years, with Marfan's syndrome is herein reported. In contrast to the adult with Marfan's syndrome who often, at a glance, shows the classical features of the disease; diagnosis of arachnodactyly in infancy and childhood is apparently more subtle. Indeed, the discovery of the aortic sinus dilatations occurred during studies to determine the cause of the cardiac murmurs and enlargement and was an important factor in establishing the diagnosis of Marfan's syndrome.

Case Reports

On April 20, 1956, identical Caucasian twin females, aged 2 years, were admitted for study because of the finding of heart murmurs. The mother stated that she had had an uneventful pregnancy, although mild ankle edema occurred during the last trimester. Birth of the twins was at full term and uncomplicated; forceps were used in the delivery. Cyanosis and anomalies were not noted and the infants were well developed and nourished; the birth weights were 7 pounds, 12 ounces and 7 pounds, 9 ounces respectively. The children had no feeding problems, gained weight, developed normally, and walked at 16 months. At the age of 19 months, the first born (E. N.) developed an acute upper respiratory infection with fever and on examination was found to have a heart murmur. Examination of the twin (B. N.) also disclosed a murmur. Four siblings and the father (the mother is pregnant and at term) have been examined. Three siblings and the father have apical systolic murmurs, left ventricular enlargement, and left axis deviation of the electrocardiogram.

Case 1 (E. N.). Physical examination revealed a well developed child; weight and height 30½ pounds, 40 inches. The head was slightly dolichocephalic and the palate was mildly arched. The fingers were somewhat slender and long. Eye examination disclosed bilateral subluxation of the lenses and myopia. There was no deformity of the thorax or spine. The lungs were clear. Examination of the heart showed the position of maximum impulse to be in the fourth intercostal space, just medial to the midclavicular line. A short systolic murmur (grade II) was heard along the left side of the sternum at the fourth interspace. The blood pressure was 96/60.

Laboratory data were as follows: erythrocytes 3.9 mil./mm.^{3}; hemoglobin, 11 Gm./100 ml.; hematocrit, 37 per cent. The electrocardiogram showed left axis deviation and left ventricular hypertrophy with horizontal position of the heart. There were biphasic and inverted T waves in the precordial leads, V_3 to V_6. The QRS complexes in all leads were normal. X-ray examination of the chest (figs. 1*A*, *B*) showed enlargement of the left ventricle. Right heart catheterization revealed normal right atrial, ventricular, and pulmonary artery

From St. Francis Hospital and Sanatorium, Roslyn, N. Y.

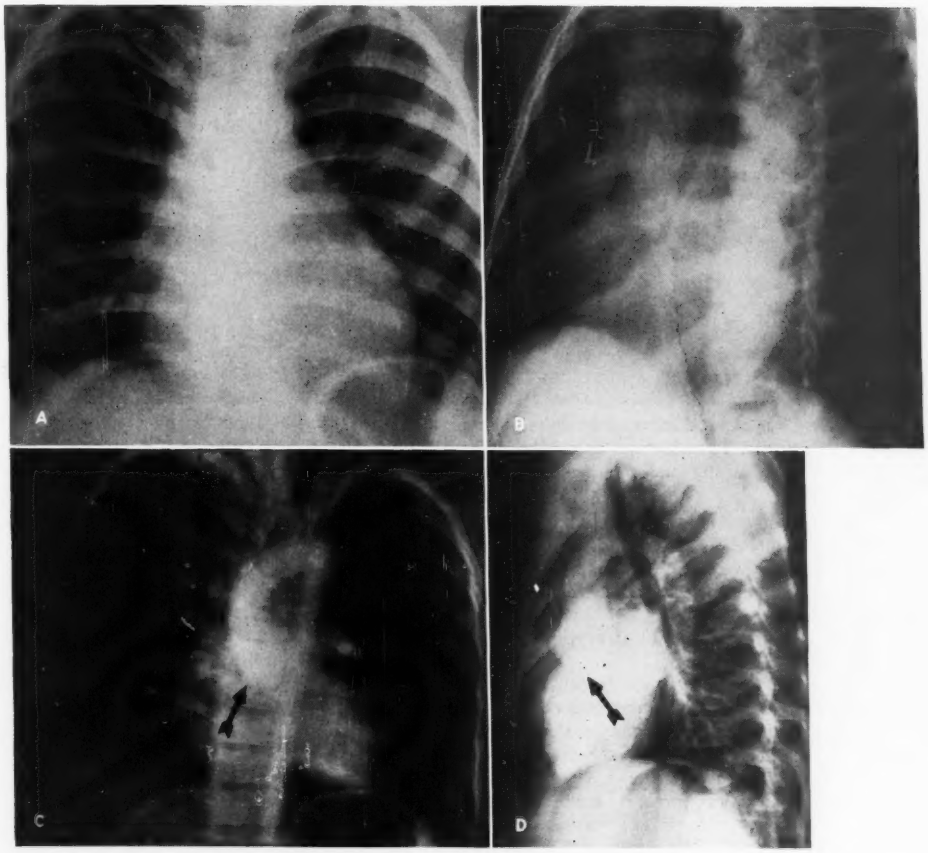

FIG. 1 (Case 1). *A*. Frontal teleroentgenogram shows an enlarged heart, especially the left ventricle. The sternum and spine are normal. *B*. Left anterior oblique view also reveals the prominent and enlarged left ventricle. *C*. Frontal angiocardiogram shows an enlarged left ventricle (chamber) and aneurysmal dilatation of the aortic sinuses (*arrow*). *D*. Left anterior oblique angiocardiogram also demonstrated the dilated aortic sinuses (*arrow*).

TABLE 1.—*Cardiac Catheterization Data of Identical Twins with Marfan's Syndrome*

	Case 1		Case 2	
Location	O_2 content (Vol. %)	Pressure (mm. Hg)	O_2 Content (Vol. %)	Pressure (mm. Hg)
SVC	9.8		9.9	
RA	9.7	1	9.8	0
RV	9.7	15/1	9.9	12/2
PA	10.2	13/5.5	9.7	12/4.5
LA			13.8	5
LV			13.8	69.3/3.3
FA	12.3			

pressures; the blood oxygen contents were normal (table 1). Angiocardiography disclosed aneurysmal dilatation of the aortic sinuses and moderate enlargement of the left ventricle (figs. 1*C*, *D*).

Case 2 (*B. N.*) Physical examination revealed a well developed and nourished child; weight, 30¼ pounds and height, 39¾ inches. The skull was slightly dolichocephalic, the palate was mildly arched, and the fingers were also somewhat thin and long. There were bilateral dislocation of the lenses and myopia. The lungs were clear and there was no thoracic deformity. The position of maximal impulse of the heart was in the fourth left intercostal space just lateral to the midclavicular line. The pulmonic

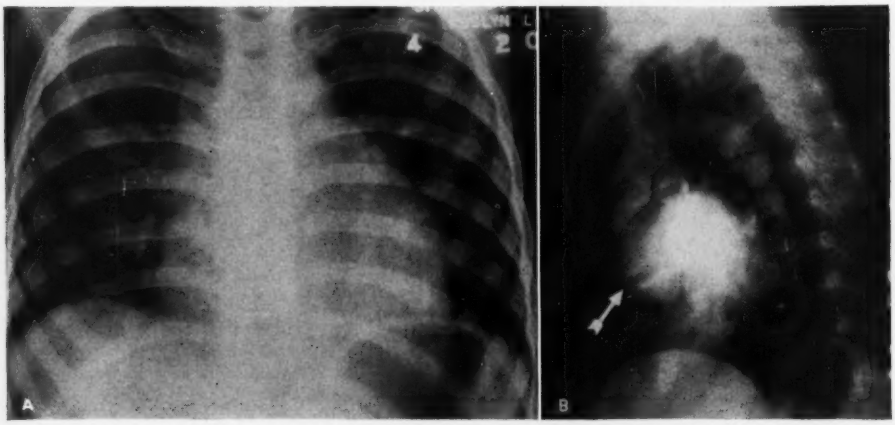

FIG. 2 (Case 2). *A*. Frontal teleroentgenogram shows an enlarged heart with enlargement of the left ventricle. Thoracic and spinal deformities are absent. *B*. Left anterior oblique angiocardiogram reveals aneurysmal enlargement of the aortic sinuses (*arrow*).

second sound was loud and snapping in character and greater than the aortic second sound. A systolic murmur (grade III) was heard along the left sternal border, maximal at the apex. The blood pressure was 100/60.

Laboratory data were as follows: erythrocytes, 3.8 mil./cu. mm.; hemoglobin, 10 Gm./100 ml.; hematocrit, 33 per cent. The electrocardiogram disclosed left axis deviation, left ventricular hypertrophy and horizontal position of the heart. X-ray examination of the heart (fig. 2*A*) showed enlargement of the heart, especially the left ventricle. Right heart catheterization pressure studies were normal. The blood oxygenation studies were also normal and there was no evidence of a right-left or left-right heart shunt. During cardiac catheterization the catheter was passed through the foramen ovale into the left atrium, across the mitral valve and into the left ventricle (pressure 69.3/3.3 mm. Hg) (table 1, fig. 3). Angiocardiography (fig. 2*B*) revealed aneurysmal dilatation of the aortic sinuses and moderate enlargement of the left ventricle.

DISCUSSION

Marfan's syndrome is a rare hereditary disease of unknown etiology. It has become recognized as a heritable disease of connective tissue.[3–8] Marfan in 1896,[10] described the first case and called attention to the long thin spider-like appearance of the extended extremities; a characteristic feature of the disease that has become known as arachnodactyly.[11] The experimental production of kyphoscoliosis, periosteal new-bone formation, and dissecting aneurysms of the aorta in growing rats fed diets containing 50 per cent sweet pea seeds is believed to be due to defective formation or excessive destruction of the chondroitin sulfate of the ground substance.[12, 13] The presence of similar lesions in arachnodactyly suggests that it may be due to a hereditary defect in chondroitin sulfate metabolism.

The patients with classical Marfan's syndrome can often be recognized at a glance. They are unusually tall, slender, and lanky with dangling, thin, spider-like limbs. In addition to dolichocephalic skulls, the ears are often long and large; the long faces topped by heavy thick glasses give them a wise and prematurely old appearance. Skeletal deformities due to poorly developed and relaxed ligaments, subcutaneous tissues, and muscles cause spinal and thoracic deformities such as scoliosis, kyphosis, funnel and pigeon breast. Hyperextension and "double jointedness" of the extremities are common. Ocular abnormalities are also prevalent occurring in up to 80 per cent of the cases.[14] Congenital bilateral dislocation of the lens due to poor ligamentous support and myopia cause serious progressive deterioration in vision.

In contrast, our patients were well developed and nourished. Only mild dolichocephalic skulls, slightly arched palates, and somewhat long and thin fingers were present. There was no history of disturbance of vision and ophthal-

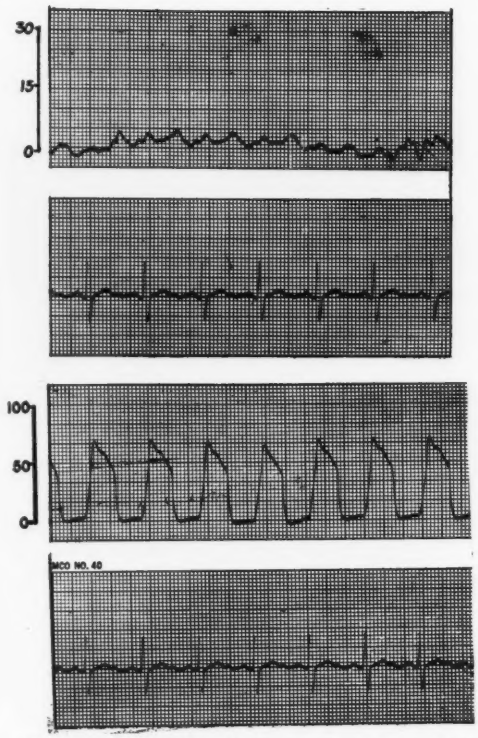

FIG. 3. *Top set.* Left atrial pressure (upper tracing) secured by right heart catheterization through a patent foramen ovale. There is a narrow atrial pulse, no systolic peak, and normal atrial mean pressure, which exclude dynamically significant mitral regurgitation. Lower tracing is simultaneous lead II of the electrocardiogram. *Bottom set.* Left ventricular pressures showing normal systolic and diastolic pressures (upper curve), ruling out significant aortic stenosis. Lower curve is simultaneous lead II of the electrocardiogram.

mic examination, made after the discovery of aortic sinus aneurysms, disclosed the edges of the ectopic lenses and established the presence of bilateral dislocated lenses and myopia.

Over 350 cases of arachnodactyly have been reported. The incidence of cardiovascular involvement is uncertain, but is estimated as being 30 to 60 per cent. The clinical cardiovascular manifestations of arachnodactyly have been thoroughly reviewed in the literature.[1, 4, 5, 15–18] Baer, Taussig, and Oppenheimer[19] were the first to call attention to cardiovascular involvement at necropsy: medial degeneration of the aorta producing aneurysmal dilatation of the ascending aorta, endocardial valvular thickening, and marked cardiac hypertrophy. Reports of sudden death due to rupture of dissecting aneurysms then followed.[20] Medial degeneration, aneurysmal dilatation and rupture of the pulmonary artery have also been recorded.[4, 5, 19, 21]

Endocardial lesions were reported in over two thirds of the autopsied cases and involved the mitral valve more often than the aorta, although combined lesions of both valves were frequent.[18] Fibromyxomatous valvular thickening has also been a common finding but is not peculiar to arachnodactyly.[3, 4, 8] It produces deformities of the valves and may be responsible for murmurs. Often the auscultatory findings are attributed to rheumatic fever. Necropsy studies, however, do not reveal the changes of rheumatism.[4, 5, 8, 18] Cardiac enlargement has been a constant finding.

Both our patients had systolic murmurs and left ventricular enlargement. In one (case 2), a patent foramen ovale permitted pressure readings across the mitral valve. Absence of a systolic peak in the left atrial curve, normal mean pressure, and narrow atrial pulse pressure were evidence against significant mitral insufficiency (fig. 2*C*). A left ventricular pressure of 69.3/3.3 mm. Hg excluded the presence of significant aortic stenosis (fig. 2*D*). The exclusion of significant mitral and aortic valvular disease also makes it probable that the cardiac enlargement is a reflection of endocardial or subendocardial disease of the left ventricle.

The aneurysmal dilatation of the aortic sinuses in the twins reported above are the sixth and seventh cases in Marfan's syndrome discovered by angiocardiography. Three were previously reported.[1] Two additional cases (aged 21 and 23 respectively) have since been found. Only 1 patient of the 7 had associated aortic regurgitation with an aortic diastolic murmur.[1] The others had apical systolic murmurs varying from grade II to IV; all but 2 had cardiac enlargement.[1, 22] It would appear that aortic sinus dilatation is probably common in Marfan's syndrome and may be part of the generalized medial aortic and pulmonary arterial degeneration that occurs in this disease.[4] The demonstration of aortic sinus dilatation

early in life also suggests that the lesion is probably primary rather than aggravated by aortic stress.[5] The prognostic significance of an aortic sinus aneurysm in arachnodactyly is unknown because discovery during life has only recently been made. Only 1 patient has had disabling symptoms during a 2-year period of observation.

Summary

Identical twins, aged 2 years, with cardiac enlargement and murmurs were found to have aneurysmal dilatation of the aortic sinuses and left ventricular enlargement after angiocardiography. Because of these findings, the significance of mild dolichocephaly of the skull, arched palate, and slender fingers was recognized; ophthalmic examination then confirmed the typical bilateral dislocation of the lenses and myopia of Marfan's syndrome.

Right heart catheterization studies in one twin were normal. In the other, the right heart catheterization findings were also normal but a patent foramen ovale permitted left atrial and ventricular pressure determinations. These disclosed an absent left atrial systolic pressure peak, a normal mean pressure, and a narrow atrial pulse pressure, which excluded significant mitral insufficiency. Aortic valvular stenosis was also excluded by the left ventricular pressure reading of 69.3/3.3. The studies suggest that left ventricular enlargement may be due to endocardial disease of the ventricle, not an uncommon finding in necropsy reports of Marfan's syndrome. The discovery of aortic sinus dilatations very early in life also indicates that medial degeneration of the aortic sinuses occurs early and does not develop in response to aortic stress. Not enough time has elapsed to judge the prognostic significance of aneurysmal dilatation of the aortic sinuses in arachnodactyly.

Summario in Interlingua

Angiocardiographia resultava in le constatation de dilatation aneurysmal del sinuses aortic e del ventriculo sinistre in bienne geminos con allargamento e murmures cardiac. Iste constatationes inspirava le correcte interpretation del presentia de leve grados de dolichocephalia, de palatos arcate, e de digitos attenuate. Le subsequente examine ophthalmic revelava le expectate dislocation bilateral del lentes e le myopia que es typic de syndrome de Marfan.

Studios a catheterisation dextero-cardiac in un del geminos esseva normal. In le altere patiente, le catheterisation dextero-cardiac etiam resultava in observationes normal, sed un patente foramine oval permitteva determinationes del pressiones sinistro-atrial e ventricular, e istos revelava le absentia de un agulia de pression systolic sinistro-atrial, un normal pression medie, e un stricte pression pulsari atrial, excludente le possibilitate de grados significative de insufficientia mitral. Stenosis del valvula aortic esseva etiam excludite super le base del lectura de un pression sinistro-ventricular de 69, 3/3,3.

Le studios suggere que allargamento sinistro-ventricular pote resultar de morbo endocardial del ventriculo. Le constatation de morbo endocardial del ventriculo non es incommun in reportos necroptic de patientes con syndrome de Marfan. Le discoperta de dilatation del sinuses aortic a un juvenissime etate etiam indica que le degeneration medial del sinuses aortic occurre precocemente e non como responsa a stresses aortic. Ha non ancora venite le tempore pro judicar del signification prognostic de dilatation aneurysmal del sinuses aortic in arachnodactylia.

REFERENCES

[1] Steinberg, I., and Geller, W.: Aneurysmal dilatation of the aortic sinuses in arachnodactyly: Diagnosis during life in three cases. Ann. Int. Med. **43:** 120, 1955.

[2] Weill, G.: Ectopie des cristallins and malformations generales. Ann. d'ocul. **169:** 21, 1932.

[3] Moses, M. F.: Aortic lesions associated with arachnodactyly. Brit. M. J. **2:** 81, 1951.

[4] Tung, H. L., and Liebow, A. A.: Marfan's syndrome. Observations at necropsy with special reference to medionecrosis of the great vessels. Lab. Invest. **1:** 382, 1952.

[5] McKusick, V. A.: The cardiovascular aspects of Marfan's syndrome: A heritable disorder of connective tissue. Circulation **11:** 321, 1955.

[6] Amundsen, P., and Holter, I.: Cardiovascular changes in dystrophia mesodermalis congenita Marfan. Acta radiol. **45:** 365, 1956.

[7] Weve, H.: Über Arachnodaktylie (Dystrophia

Mesodermalis Congenita, Typus Marfan). Arch. Angenk. **104:** 1, 1931.

[8] Sloper, J. C., and Storey, G.: Aneurysms of the ascending aorta due to medical degeneration associated with arachnodactyly (Marfan's disease) J. Clin. Path. **6:** 299, 1953.

[9] Black, H. H., and Landay, L. H.: Marfan's syndrome: Report of five cases in one family. Arch. Dis. Child. **89:** 444, 1955.

[10] Marfan, A. B.: Un cas de deformation congenitale des quatre membres, plus prononcee aux extremeties, characterisee par l'allongement des os avec un certain degre d'amincissement. Bull. et mém. Soc. méd. hôp. Paris **13:** 220, 1896.

[11] Archand, M. C.: Arachnodactylie. Bull. et mém. Soc. méd. hôp. Paris **19:** 834, 1902.

[12] Ponseti, I. V., and Shepard, R. S.: Lesions of the skeleton and of other mesodermal tissues in rats fed sweet-pea (lathyrus) adoratus seeds. J. Bone & Joint Surg. **36-A:** 1031, 1954.

[13] Bean, W. B., and Ponseti, I. V.: Dissecting aneurysm produced by diet. Circulation **12:** 185, 1955.

[14] Rados, A.: Marfan's syndrome (arachnodactyly coupled with dislocations of the lens). Arch. Ophth. **27:** 477, 1942.

[15] Tobin, J. R., Bay, E. B., and Humphreys, E. M.: Marfan's syndrome in the adult (dissecting aneurysm of the aorta associated with arachnodactyly). Arch. Int. Med. **80:** 475, 1946.

[16] Uyeyama, H., Kondo, B., and Kamins, M.: Arachnodactyly and cardiovascular disease: Report of an autopsied case with a summary of previously autopsied cases. Am. Heart J. **34:** 580, 1947.

[17] Marvel, R. J., and Genovese, P. D.: Cardiovascular disease in Marfan's syndrome. Am. Heart J. **42:** 814, 1951.

[18] Goyette, E. M., and Palmer, P. W.: Cardiovascular lesions in arachnodactyly. Circulation **7:** 373, 1953.

[19] Baer, R. W., Taussig, H. B., and Oppenheimer, E. H.: Congenital aneurysmal dilatation of the aorta with arachnodactyly. Bull. Johns Hopkins Hosp. **72:** 309, 1943.

[20] Etter, L. E., and Glover, L. P.: Arachnodactyly complicated by dislocated lenses and death from rupture of dissecting aneurysm. J.A.M.A. **123:** 88, 1943.

[21] Anderson, M., and Pratt-Thomas, H. R.: Marfan's syndrome. Am. Heart J. **46:** 911, 1953.

[22] Steinberg, I., and Finby, N.: Clinical manifestations of the unperforated aortic sinus aneurysm. Circulation **14:** 115, 1956.

Hippocrates

He was the son of a famous priest-physician at an asclepieion at Kos. He grew up in a medical atmosphere and studied medicine from early childhood. He studied in all the known centers of learning, even in Egypt. This required twenty years after what corresponds to our college. Mature in years, filled with the learning of all peoples of his time, rich in experience and observation, he returned to his native island to teach and practice medicine. Hippocrates systematized all rational practices of his time. He finally and completely divorced medicine from religion. He introduced the bedside method of medicine. He introduced physical examination as an aid to diagnosis. He crystallized and formulated the code of medical ethics known as the Hippocratic oath, which is one of the most complete ethical or moral codes ever set down. He was a great writer and many of his books were the last word of authority in the most advanced medicine for over two thousand years. He recognized the real position of the physician. He said, "The physician is the hand-maiden of Nature," and that he can but assist her.

Hippocrates lived during the age of Pericles, Aristophanes, Praxiteles, Socrates, and Plato. The time, in short, which marks the highest peak in civilization among Western peoples, the excellence of which we are in many ways beginning to appreciate and of which in many ways we have not equaled even today.—L. A. Turley. *The History of the Philosophy of Medicine.* Norman, University of Oklahoma Press, 1935.

Ventricular Septal Defects in the Infant Age Group

By STELLA C. ZACHARIOUDAKIS, M.D., KORNEL TERPLAN, M.D., AND EDWARD C. LAMBERT, M.D.

An analysis was made of the 23 cases of isolated ventricular septal defects seen at autopsy over a 20-year period at a children's hospital. All of the deaths occurred during the first 15 months of life. In addition to the clinical and morphologic findings, cardiac catheterization data obtained on 6 of the infants are presented. A wide range of electrocardiographic variation with respect to ventricular hypertrophy was found. No simple relationship between the size of the defect and the clinical manifestations could be demonstrated. The surgical implications of the findings are discussed.

RECENTLY a few authors[1-3] have recognized uncomplicated ventricular septal defects to be a major cause of heart failure and death in the infant age group, particularly in the early months of life. However, there are little data concerning the relative frequency of this malformation as compared with other serious cardiac anomalies and even less regarding the findings obtained at cardiac catheterization in cases of ventricular septal defect subsequently proved at autopsy. The purpose of this communication is to analyze a series of such cases from statistical, clinical, hemodynamic, and morphologic points of view and to discuss their surgical implications.

MATERIAL AND METHOD

A review of 2,586 consecutive autopsies performed at the Children's Hospital of Buffalo during the period of 1936 to 1956 revealed 288 cases of major congenital cardiac anomalies. Twenty-three of these proved to be uncomplicated ventricular septal defects. For the purposes of this study, stillborn infants and clinically unimportant cardiac abnormalities were excluded. In this series of ventricular septal defects the foramen ovale was closed in only one. However, in no instance did its valve appear incompetent. Two hearts with associated widely patent ducti were retained in this study. One of these occurred in a newborn baby who died at 3 days of age; the other in a baby who died on the eleventh day. In both, the patency of the ductus arteriosus was considered to be in the range of normal.[4] In all other cases the ducti were either closed or very small.

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The following additional cardiovascular anomalies were noted: left superior vena cava entering coronary sinus (cases 13 and 18); right aortic arch (case 5); bicuspid aortic and pulmonic valves (case 4). We did not think that these abnormalities had affected the clinical course of these patients.

Cardiac catheterization was performed on 6 of the infants in the usual fashion, with a Sanborn Poly-viso direct writing recorder and Statham strain gages as pressure transducers. In each patient light general anesthesia with intravenous pentothal was employed in addition to local procaine anesthesia and premedication. The catheter was introduced into a vein in the groin (saphenous or femoral). Blood gases were analyzed by the Van Slyke method. Because of the size and condition of the patients we were unable to obtain respiratory gases. It is necessary to point out that all of the infants were ill and in varying degrees of heart failure at the time of the cardiac catheterization. In 2 of them it was found necessary to administer 100 per cent oxygen by mask during the procedure. No calculations of shunts or flows were made because we thought that, under the circumstances, the errors inherent in the assumptions that must be made were too great.

Special attention was given to the histologic findings in the lungs in an effort to determine vascular changes. The blood vessels were specifically studied in regard to changes in their walls. In addition to the usual hematoxylin-eosin stain, the orcein-Van Gieson method was used for elastic tissues and the smooth musculature in the blood vessels in all sections from the lungs.

As long as there is no standard measurement applied by all who are interested in the study of the relation between lumen and thickness of arterial walls containing elastic membranes, it seemed better to go by general comparisons of the individual cases, with assumed normal controls of the same age in this entire series. A variety of factors intrinsic in the lung tissue at the time of death (like atelectasis, pneumonitis, hemorrhage, edema, and, in particular, emphysema) and extrinsic factors of a technical nature, such as interval between time of death and postmortem examination, type of fixation, embedding material, and processing (in-

TABLE 1.—*Relative Frequency of the Common Major Congenital Malformations of the Heart in Infants and Children as Seen at Autopsy*

	Number of cases	Approximate per cent
Complete transposition of the great vessels	35	12
Ventricular septal defect	23	8
Tetralogy of Fallot	23	8
Primary endocardial fibroelastosis	21	7
Persistent ostium atrioventriculare commune	18	6
All others	168	59
Total	288	100

cluding the temperature used for stretching the paraffin sections) should be considered in any thorough evaluation. The most important facet, however, would be to agree on specified areas in the lung tissue for examining the blood vessels and, in particular, on the planes in which such blocks including the small arteries and their branches should be cut. Under such conditions, the direct measuring of numerous representative vessels appears preferable to the more general comparisons that we have used in this study.

RESULTS

Clinical Aspects. For purposes of comparison, an analysis was made of the 288 major cardiovascular anomalies revealed at autopsy. The relative frequency of the 5 most common in this series is presented in table 1. Ventricular septal defects proved to be a common cause of death in congenital heart disease. While it must be admitted that in 8 cases death followed unsuccessful surgery, such surgery was only performed out of desperation on infants otherwise expected to die in a short time.* Also, with the exception of primary endocardial fibroelastosis, a similar proportion of fatalities occurred following surgery in each of the other major malformations listed in table 1.

* The surgical procedures were as follows: Closure of the defect under direct vision with the aid of hypothermia (cases 12, 13 and 15); creation of pulmonic stenosis to reduce pulmonary hypertension and flow (cases 11 and 14); and ligation of ductus arteriosus (cases 1, 6, 9). In the last 3 it was mistakenly thought that a widely patent ductus might be present, causing part of the load on the infant's heart.

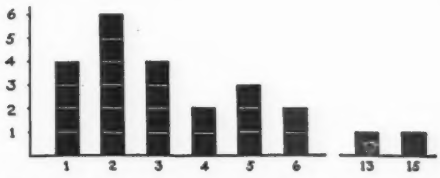

FIG. 1. Age in months (*abscissa*) at death in 23 cases of ventricular septal defect.

The ages of the patients at death varied from 3 days to 15 months. Twenty out of 23 deaths occurred during the first 6 months of life (fig. 1). The majority of the patients died during the first 3 months.

The clinical symptoms and physical findings were similar to those described by Engle[1] in 9 infants who died with uncomplicated ventricular septal defects. Failure to gain and recurrent episodes of respiratory infections were the chief complaints in all 23 cases. In 7, ranging in age from 3 weeks to 5 months, the admission weight was the same or less than the birth weight. Respiratory distress associated with transient cyanosis was present in all. In 4 cases there was a history of cyanotic spells usually occurring during feedings. These episodes preceded the development of respiratory distress or infection. A loud, harsh, prolonged systolic murmur, maximal along the lower left sternal border and accompanied by a systolic thrill, was present in 21 cases. There was no murmur in 1 instance (case 21), a newborn who died at 3 days. One patient, (case 16) was dead on arrival; hence, there were no data regarding the presence or absence of a murmur. Evidence of both right and left-sided congestive heart failure as manifested by dyspnea, rales, and hepatic enlargement was present on admission in 19 of the 23 cases. Peripheral edema was never manifest. In 7 cases the birthweight was less than 2500 Gm. A history of German measles in the first trimester of pregnancy was given in case 3.

Roentgenographic examination, which was performed in 17 cases, revealed cardiac enlargement of a moderate to marked degree in all. Increased hilar vascular markings and convexity of the pulmonary segment were invariably present. Radiologic evidence of left atrial enlargement was present in 6 of the 12 patients

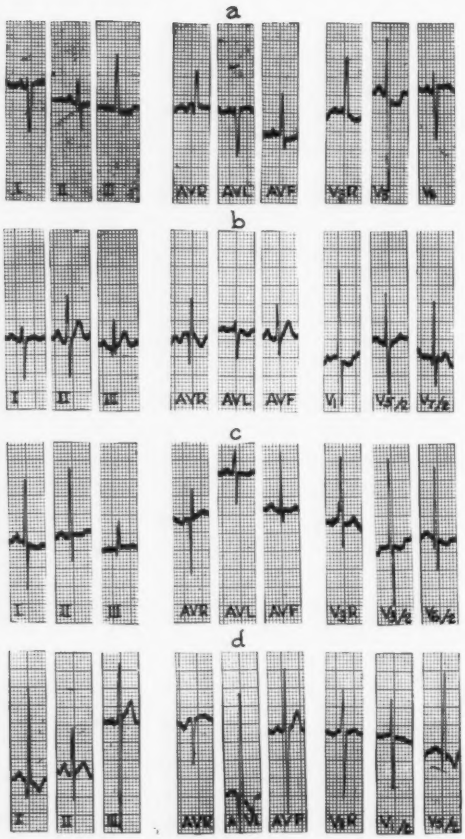

FIG. 2. Representative electrocardiograms showing variability of findings with respect to evidence of ventricular hypertrophy. Cardiac catheterization was performed on each of these infants. *a*. Case 12, age 3 weeks, right ventricular hypertrophy. *b*. Case 15, age 6 months, combined ventricular hypertrophy. *c*. Case 13, age 2 months, combined ventricular hypertrophy. *d*. Case 10, age 5 weeks, left ventricular hypertrophy.

in whom fluoroscopic examination was done. In case 14 there was a complete collapse of the left lung, which re-expanded spontaneously in 6 days.

Electrocardiographic tracings, including precordial leads, were available in 15 patients (fig. 2 and table 2). None of the tracings were normal.* In 7 there was evidence of right ventricular hypertrophy manifested by an abnormally tall and usually delayed R wave in precordial positions V_1 and V_{3R}, together with the progressive decrease in the R wave and increase in the S wave as the electrodes were moved to the left precordium ("Wilson phenomenon"). Miller[6] has stressed the value and consistency of the latter finding in the diagnosis of right ventricular hypertrophy in small infants beyond the age of 1 week. Two electrocardiograms showed definite evidence of left ventricular hypertrophy manifested by abnormally tall R waves in V_5 and V_6 with depressed S-T segments and inverted T waves in the same leads. Six of the tracings revealed evidence of combined ventricular hypertrophy. This diagnosis was made whenever patterns of both right and left ventricular hypertrophy appeared in the same electrocardiogram. In 3 of these 6 electrocardiograms the evidence of left ventricular hypertrophy was more marked than that of right ventricular hypertrophy; in the other 3 the reverse was true.

Physiologic Aspects. The results of the data obtained at cardiac catheterization in 6 patients are summarized in table 3. In 4 of the infants the catheter was directed in the usual fashion through the right atrium and right ventricle, into the pulmonary artery. In the other 2 it passed from the right ventricle directly into the aorta (fig. 3). (It was not possible subsequently to direct the catheter into the pulmonary artery in either of these 2 patients.) In no instance was a significant pressure gradient present across the aortic or pulmonary valves.

The systolic pressure in the right ventricle was markedly elevated in all patients. In 5 of them it was equivalent to the systemic systolic pressure. In the sixth patient it was lower than the systemic pressure. No wedge pressures were obtained.

Evidence of a left-to-right shunt at the atrial level with a rise in oxygen content of the venous blood obtained from the right atrium occurred in 3 patients. The magnitude of these rises exceeded 2 volumes per cent. In all 6 patients there was a rise in the blood oxygen content at the ventricular level exceeding 1 volume per cent. The oxygen saturation of the arterial blood obtained from the aorta or femoral artery was below 90 per cent in 3

* Normal values were determined according to Ziegler.[5]

TABLE 2.—*Electrocardiographic and Postmortem Findings in Twenty-three Cases of Uncomplicated Ventricular Septal Defects*

Case	Age	Electrocardiogram	Ventricular wall thickness (mm.)		Ventricular septal defect diameter (mm.)	Ratio of size septal defect to aortic orifice	Medial hypertrophy of the small pulmonary arteries
			Right	Left			
1. C. P.	3 mos.	CVH	3	9	4	0.42	Slight
2. F. C.	1 mo.	RVH	4	6	4	0.6	Distinct
3. K. B.	6 wks.	RVH	7	6	7	1.35	Not significant
4. J. R.	11 das.	RVH	8	6	12	2.2	Distinct
5. J. F.	3 mos.	RVH	11	9	9	1.2	Distinct
6. K. M.	3 mos.	CVH	7	9	10	1.2	Distinct
7. W. A.	2 mos.	RVH	8	9	3	0.27	Slight
8. M. M.	3½ mos.	CVH	5	6	10	1.1	Distinct
9. B. H.	2 mos.	LVH	8	10	10	1.25	Distinct
10. A. M.†	3 mos.	LVH*					Data unavailable
11. L. K.	5 mos.	CVH*	7	9	10	1.25	Distinct
12. G. C.	6 wks.	RVH*	10	7	5	0.71	Distinct
13. H. G.	2 mos.	CVH*	8	9	10	1.16	Not significant
14. K. S.	5 mos.	CVH*	3	8	7	0.55	Not significant
15. L. S.	6 mos.	RVH*	11	10	6	0.75	Distinct
16. T. C.	6 mos.		8	8	19	2.0	Distinct
17. S. S.	15 mos.		4	9	5	0.42‡	Not significant
18. D. P.	6 wks.		6	8	"large"		Slight
19. R. M.	5 mos.		10	9	8	1.0	Distinct
20. D. B.	13 mos.				10	0.89‡	Distinct
21. D. F.	3 das.				9	1.8	Not significant
22. A. D.	2 mos.		4	6	6	0.86‡	Not significant
23. J. M.	4 mos.		6	5	3	0.38‡	Data unavailable

* Cardiac catheterization performed.
† Autopsy performed at outside hospital. No measurements given. Two defects present.
‡ Aortic orifice not measured. Described as normal. Average normal measurement for age used.

TABLE 3.—*Data Obtained at Cardiac Catheterization: Six Proved Cases of Uncomplicated Ventricular Septal Defect*

Case no.	Age	Pressures (mm. Hg)					Per cent oxygen saturation							Capacity (O_2) ml./L.
		Aorta	FA	PA	RV	RA	Aorta	FA	PA	RV	RA	SVC	IVC	
10	3 mos.		89/52		92/0	9/0		83		83	59	50	37	167
											77			
11	5 mos.		104/73	108/50	108/0	5/0		88	79	80	64	40	39	129
										67				
12	1 mo.	99/42			99/0	8/0				82	43	42		142
										64				
13	2 mos.	104/60	125/62		104/0	12/0	87			73	39	37		123
14	5 mos.		75/50	70/37	82/0			98*	89	87	65	41	54	150
										62	51			
15	6 mos.		102/57	75/23	75/0	5/0		94*	93	96	70	72	49	122

FA = Femoral artery; PA = Pulmonary artery; RV = Right ventricle; RA = Right atrium; SVC = Superior vena cava; IVC = Inferior vena cava.
* One hundred per cent oxygen administered throughout procedure.

patients with a lowest value of 83 per cent. Two patients showed normal peripheral arterial oxygen saturation. However, 100 per cent oxygen was administered throughout the procedure to both of them because of their poor clinical condition (the ear-oximetry readings were 66 and 68 per cent at the beginning of the procedure). It is clear that no conclusions re-

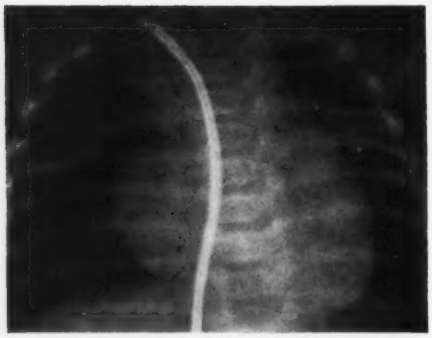

FIG. 3. Roentgenogram showing that catheter has been directed from inferior vena cava through right atrium and right ventricle, into aorta and innominate artery.

garding the presence or absence of a right-to-left shunt can be drawn in these 6 infants. Both the existence of congestive heart failure and the use of a general anesthetic could easily explain the unsaturated state of the arterial bloods.

Morphologic Aspects. All of the 23 hearts examined were enlarged, showing both dilatation and hypertrophy. This enlargement, in all but 1 instance (case 10) involved chiefly the right heart. Admittedly, measurement of the thickness of the ventricular wall offers only a rough estimate of the degree of its hypertrophy, particularly in the presence of varying degrees of ventricular dilatation (table 2). Dilatation of the pulmonary artery was a constant finding. The aorta appeared normal in all except case 10 in which it was dilated. Pulmonary congestion, which was frequently marked and associated with patchy atelectasis, was an almost constant finding. The liver was usually hyperemic but of a lesser degree than the lungs.

The defects ranged in size from 3 to 19 mm. (table 2 and fig. 4). According to the recent classification outlined by Becu and associates[7] their location on the septum was as follows: In 17 cases the defect was in the region of the outflow tracts posterior to the crista supraventricularis and below the right and posterior aortic cusps (usually described as the region of the membranous septum). In this group there were 2 examples (cases 5 and 10) of double openings. In both of these hearts there was a second defect in the region of the inflow

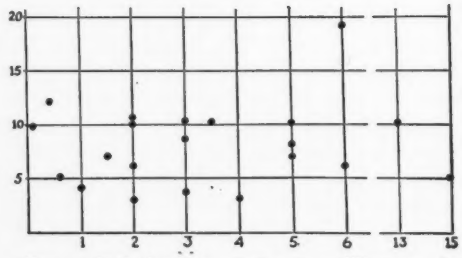

FIG. 4. Relationship of size in millimeters (*ordinate*) of ventricular septal defect to age in months (*abscissa*) at death.

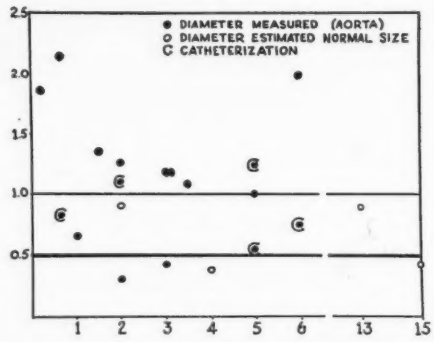

FIG. 5. Relationship of relative size of ventricular septal defect (*ordinate*) to age in months (*abscissa*) at death. (Relative size determined by ratio of diameter of defect to diameter of aortic orifice.)

tracts under the posterior and septal leaflets of the tricuspid valve. In cases 2 and 23 the defects were small (4 mm. and 3 mm., respectively) and were located in the region of the outflow tracts anterior to the crista supraventricularis just below the pulmonary valve. In cases 6 and 9 there were large (10 mm.) openings involving the apical portion of the ventricular septum. In order to determine the relative size of the defect the ratio of its diameter to that of the aortic orifice was calculated in the 21 cases where measurements were available (table 2 and fig. 5).

Noncardiovascular congenital malformations were present in 5 patients. They included right hydronephrosis and hydroureter, absence of the left kidney and ureter, hypospadias, mongolism, and oxycephalus. It was considered that in none of these cases had the associated lesion contributed to the death of the infant.

Examination of the small pulmonary arteries

in 21 cases revealed distinct abnormal medial hypertrophy in 12 and slight in 3 (table 3). In the remaining 6 cases no significant changes were seen as compared with the normal controls. Endarteritic intimal thickening was not observed in any one of the total series.

Discussion

Clinical Aspects. Our data regarding the frequency with which a ventricular septal defect may cause heart failure and death in the early months of life correspond roughly with those recently reported by others. Harned and associates[2] found 5 cases of this anomaly among 55 congenital cardiac malformations taken from the protocols of 1,400 consecutive autopsies in a large general hospital. All 5 of the patients died before the age of 15 months. Edwards[8] noted that of the 30 specimens of ventricular septal defects in the collection of the Mayo Clinic, 19 were from infants who died before the age of 6 months. Marquis[3] found it to be the most common malformation in 110 consecutive cases of congenital heart disease seen at autopsy during the first 3 years of life.

We do not wish to infer that heart failure due to this malformation necessarily carries a fatal outlook in early infancy. In the past 5 years we have observed 4 patients with similar signs, symptoms, and electrocardiographic and roentgenographic findings who survived congestive heart failure in early infancy and appear clinically much improved at ages varying between 2 and 4 years. Cardiac catheterization performed on these patients during the first year of life revealed essentially the same findings as in the 6 patients of this study: that is, marked right ventricular and pulmonary arterial hypertension approximating the systemic pressure, and a large left-to-right shunt at the ventricular level. A similar experience with 3 infants catheterized before the age of 8 months was reported by Harned's group.[2] This is, of course, in line with the concepts of Dammann and Ferencz[9] and confirms the statement of Edwards: "It appears that in those patients who survive the critical six postnatal months, adaptation to excess pulmonary flow is reasonably well-tolerated."[8]

The symptomatology, physical findings, roentgenographic data, and clinical course of these patients were essentially the same as recently described by other authors[1, 2, 9, 10] in smaller groups of infants. Ferencz and co-workers[11] and Harned and associates[2] have pointed out that these clinical findings are nonspecific and for the most part apply to other cardiac malformations that produce large hearts and increased blood flow to the lungs in infants. We have nothing to add to the discussions of the differential diagnosis presented by these 2 groups of authors. In our experience, even with cardiac catheterization, it is occasionally impossible to distinguish persistent ostium atrioventriculare commune, truncus arteriosus, patent ductus, and a single ventricle from an isolated ventricular septal defect.

We are unable to explain the variations obtained in the electrocardiograms regarding ventricular hypertrophy or to relate them to age, clinical, roentgenographic, or pathologic findings in this series of cases (table 2). Nor are the physiologic data obtained at catheterization helpful in this respect. Despite similar values as to pressures and shunts, a complete range of electrocardiographic variability with respect to right ventricular hypertrophy, combined ventricular hypertrophy, and left ventricular hypertrophy was found. Data regarding the pulmonary artery wedge pressures and the resistances in the pulmonary and systemic circuits might be helpful in this respect. The finding of Blount and co-workers[12] that a left ventricular hypertrophy pattern is associated with large left-to-right shunts in the absence of severe pulmonary hypertension does not apply to case 10 in our series. In this infant the equivalent of the systemic arterial pressure was present in the right ventricle at cardiac catheterization. In case 9, in which clear electrocardiographic evidence of left ventricular hypertrophy had been obtained, the defect was large (10 mm.) and it seems probable that a marked degree of pulmonary hypertension had been present. An additional point is that in our patients with left ventricular hypertrophy, in contrast to the older children and adults analyzed by Blount's group,[12] the T waves over the left precordium were inverted (which,

according to Cabrera and Monroy,[13] indicates systolic rather than diastolic stress).

Physiologic Aspects. It is now clear that there is an extreme range of variability insofar as pressures, volume, and direction of shunts are concerned in patients with ventricular septal defects.[12, 14, 15] The findings summarized in table 3 are from 6 infants who had manifested obvious clinical evidence of heart failure prior to catheterization. In 5 of the infants the degree of right ventricular hypertension together with the evidence of a large left-to-right shunt indicated the presence of a defect of sufficient size to equalize the pressure in the 2 ventricles and a pulmonary resistance that was less than the systemic. In cases 12 and 13 an identical systolic pressure was demonstrated by the lack of a pressure gradient between the aorta and the right ventricle when the catheter was withdrawn from this vessel into the ventricle. In the sixth catheterized case (case 15) the systolic pressure in the femoral artery was 36 per cent greater than that in the pulmonary artery. Kroeker and Wood[16] have demonstrated that the femoral artery systolic pressure may be 4 to 19 per cent greater than the central aortic pressure. If this applies to infants, it is unlikely that in this patient the aortic and pulmonary arterial systolic pressures were equivalent. In the 2 cases (11 and 14) in which data were available, the diastolic pressure in the pulmonary artery was significantly lower than that in the peripheral artery. This indicates, as Dammann and Ferencz[9] point out, that a lower peripheral vascular resistance is present in the pulmonary circuit as compared to the systemic when the systolic pressures in the 2 great vessels are the same.

The additional finding in 3 patients of a large left-to-right shunt into the right atrium should, we believe, be ascribed to functional tricuspid insufficiency* in view of the fact that no anomalies other than the ventricular septal defects were found. In no instance did it appear that the defect communicated directly with the right atrium. The existence of functional tricuspid insufficiency in the presence of a ventricular septal defect was recognized by Baldwin and associates[17] in 1945. Obviously, this finding of left-to-right shunts at both the atrial and the ventricular levels complicates the differential diagnosis. Such patients may be subjected to surgery in an attempt to repair erroneously suspected atrial septal defects. Watkins and Gross[18] report this experience with 3 patients (apparently not infants) with "adequate pre-operative catheterization studies."

Pathologic Aspects. Several authors[7, 12, 14] have accepted Selzer's contention that the size of the defect determines its clinical importance.[19] Insofar as our material is concerned, there was no apparent relationship between the absolute size of the defect and the ages at death (fig. 4). In accordance with the observation of Selzer and Laqueur[20] that the relationship of the size of the opening to the size of the aortic orifice is important, we determined the ratio of the 2 in terms of their diameters. Again, there was no apparent correlation with the ages at death (fig. 5). However, 12, or more than half, of the hearts of our series had defects as large as or larger than the aortic orifice. Also, the ratios in the catheterized cases are compatible with Selzer's reasoned assumption that when the ventricular septal defect is larger than one half of the aortic orifice the pressure differential between the 2 ventricles may disappear.[21] In all 5 catheterized patients with available autopsy measurements the ratio was greater than 0.5.

The 4 cases with small defects and ratios below 0.5 are difficult to explain. There were no apparent significant differences in the clinical, roentgenographic, electrocardiographic, or pathologic data in this group as compared with the infants who had large defects. Catheterization findings would have been most interesting in this group. Engle,[1] in her series of 9 infants, reported 1 with a defect only 2 mm. in diameter. Her suggestion that the relationship of the location of the aorta to the defect is of importance would not apply to our case 23. In this heart there was only a 3-mm. opening located just below the pulmonic valve, anterior to the crista supraventricularis.

* There, of course, exists the possibility that in life the valve of the foramen ovale was incompetent despite the fact that such was not apparent at autopsy.

Our data do serve to confirm the findings of Selzer[19] and of Becu et al.,[7] that the location of the defect in the septum is not important in determining its effect on the cardiovascular system. The 4 patients (cases 2, 6, 9, and 23) with single openings in other than the usual site were in no respect different from the other 19 infants.

In septal defects with the same systolic pressure in the pulmonic and systemic circuits Dammann and Ferencz[9] have described 3 distinct clinical syndromes or phases. Although we obviously cannot assume the same hemodynamic situation in all of our patients, it is apparent that clinically all of them fit into what these authors term "Phase I." This phase is manifested by retarded growth, recurrent pulmonary infections, dyspnea, excessive blood flow to the lungs, cardiac enlargement, and high-output cardiac failure. Adaptation and survival are ascribed largely to an increase of the pulmonary vascular resistance produced by medial hypertrophy in the small pulmonary arteries. Distinct changes of this type present in 12, or over half, of our cases suggest partial adaptation to the altered hemodynamics produced by the defect. However, analysis of the clinical data in these failed to reveal any significant differences as compared with the 6 patients in whom no significant changes in the small pulmonary arteries were found. The same holds true with respect to the age at death and onset of symptoms in our series. In all but 1 of the 9 infants reported by Engle,[1] the fetal character of the small muscular pulmonary arteries was retained. In 3 of our hearts with small defects less than half of the diameter of the aortic orifice, the pulmonary vascular changes were described as slight or not significant. This suggests the possibility that the patients involved (cases 1, 7, 17) may not have had severe pulmonary hypertension. Several of the patients with large defects, on the other hand, had either slight or no significant medial hypertrophy of the small pulmonary arteries.

Dammann and Ferencz[9] found that of a group of 27* infants who had manifested in life the clinical findings of "Phase I" and who had been shown to have equal systemic and pulmonary artery pressures, the majority had pulmonary arteries with thicker walls and smaller lumens than the average normal of the same age. (Most of them, however, fell into what was considered to be the range of normal.) Our failure to correlate the changes noted in our series with the ages at death and the clinical findings probably indicates that other factors are involved and the observed medial hypertrophy was not sufficiently marked to benefit these patients.

Surgical Implication. The data as presented have a direct bearing on the surgical approach to this problem: (1) The frequency of early death necessitates surgery in the first few months of life if a significant reduction in the fatality rate is to be achieved; (2) even in infants who survive the early months of life, pulmonary vascular changes are commencing that may well preclude surgery at a later date; and (3) the data accumulated in our series and that of Becu and co-workers[7] are indicative of the range of anatomic variations that the surgeon must be familiar with and be expected to cope with—the wide range in the size of the lesions, multiple defects, and unusual locations of the defects in the septum.

Summary

The clinical features and postmortem findings have been analyzed in 23 infants who had a ventricular septal defect and died in heart failure. This defect comprised 23 (8 per cent) of 288 major cardiac malformations observed at autopsy over a 20-year period at a children's hospital. The majority of the deaths occurred during the first 3 months of life.

Hemodynamic data obtained on 6 of these infants revealed a large left-to-right shunt and marked right ventricular and pulmonary artery hypertension in all. In 3 of the patients the shunt appeared at the atrial as well as the ventricular level. In 5 the systolic pressure in the right ventricle was equivalent to the pressure in the systemic artery.

There was a wide variability in the electrocardiographic findings with respect to evidence of ventricular hypertrophy. Patterns of right,

* This group included single ventricle, large ventricular septal defects, and patent ductus.

left, and combined ventricular hypertrophy were found without apparent correlation with the clinical, hemodynamic, or postmortem findings.

No apparent relationship was found between the size of the defect or its location on the septum and the clinical manifestations or age at death. Four of the hearts had small defects less than half the diameter of the aortic orifice.

Distinct medial hypertrophy of the small pulmonary arteries was present in 12 cases; in 6 cases, no significant changes were seen.

The surgical implications of these findings are discussed.

Summario in Interlingua

Es analysate le aspectos clinic e constatationes post morte in le casos de 23 infantes con defecto ventriculo-septal qui moriva in disfallimento cardiac. Le 23 casos representa 8 pro cento del 288 major malformationes cardiac observate in autopsias in le curso de 20 annos a un hospital pro infantes. Le majoritate del mortes occurreva durante le prime tres menses del vita.

Datos hemodynamic disponibile in sex del casos revelava un major derivation sinistro-dextere e marcate grados de hypertension dextero-ventricular e pulmono-arterial. In tres del casos le derivation occurreva al nivello atrial tanto ben como al nivello ventricular. In cinque le pression systolic del ventriculo dextere equivaleva le pression del arteria systemic.

Le electrocardiogrammas variava grandemente quanto al presentia de signos de hypertrophia ventricular dextere, sinistre, o combinate. Iste signos non se trovava in correlation evidente con le observationes clinic, hemodynamic, e necroptic.

Esseva trovate nulle relation inter le magnitude del defecto (o su sito) e le manifestationes clinic o le etate del patiente al tempore del morte. Quatro del cordes habeva parve defectos de minus que un medietate del diametro del orificio aortic.

Distincte hypertrophia medial del minor arterias pulmonar esseva presente in 12 casos. In sex casos nulle alterationes significative esseva observate.

Es discutite le signification de iste constatationes ab le puncto de vista chirurgic.

REFERENCES

1 Engle, M. A.: Ventricular septal defect in infancy. Pediatrics **14:** 16, 1954.

2 Harned, H. S., Jr., Crothers, C. H., and Whittemore, R.: Diagnosis of atrial and ventricular septal defects. Am. J. Dis. Child. **90:** 211, 1955.

3 Marquis, R. M.: Ventricular septal defect in early childhood. Brit. Heart J. **12:** 265, 1950.

4 Christie, A.: Normal closing time of the foramen ovale and the ductus arteriosus. Am. J. Dis. Child. **40:** 323, 1930.

5 Ziegler, R. F.: Electrocardiographic Studies in Normal Infants and Children. Springfield, Ill., Charles C Thomas, 1951.

6 Miller, R. A.: The electrocardiogram in congenital malformations of the heart. Pediat. Clin. North America, 51, 1954.

7 Becu, L. M., Fontana, R. S., DuShane, J. W., Kirklin, J. W., Burchell, H. B., and Edwards, J. E.: Anatomic and pathologic studies in ventricular septal defect. Circulation **14:** 349, 1956.

8 Edwards, J. E.: Functional pathology of congenital cardiac disease. Pediat. Clin. North America 13, 1954.

9 Dammann, J. F., Jr., and Ferencz, C.: The significance of the pulmonary vascular bed in congenital heart disease. III. Defects between the ventricles or great vessels in which both increased pressure and blood flow may act upon the lungs and in which there is a common ejectile force. Am. Heart J. **52:** 210, 1956.

10 Rossi, E.: Herzkrankheiten im Säuglingsalter. Stuttgart, Georg Thieme, 1954, p. 172.

11 Ferencz, C., Johnson, A. L., and Goldbloom, A.: Problem of differential diagnosis in infants with large hearts and increased blood flow to the lungs. Pediatrics **13:** 30, 1954.

12 Blount, S. G., Jr., Mueller, H., and McCord, M. C.: Ventricular septal defect. Am. J. Med. **18:** 871, 1955.

13 Cabrera, C. E., and Monroy, J. R.: Systolic and diastolic loading of the heart. II. Electrocardiographic data. Am. Heart J. **43:** 669, 1952.

14 Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B.: Ventricular septal defect. *In* Diagnosis of Congenital Heart Disease. Chicago, Year Book Publishers, Inc., 1955, p. 254.

15 Burchell, H. B., and Wood, E. H.: The interdependence of the medical, surgical and laboratory disciplines in the selection of cases for cardiac surgery. Surg. Clin. North America, 919, 1955.

16 Kroeker, E. G., and Wood, E. H.: Comparison

of simultaneously recorded central and peripheral arterial pressure pulses during rest, exercise and tilted positions in man. Circulation Research **3:** 623, 1955.

[17] BALDWIN, E. DEF., MOORE, L. V., AND NOBLE, R. P.: The demonstration of ventricular septal defect by means of right heart catheterization. Am. Heart J. **32:** 152, 1946.

[18] WATKINS, E., JR., AND GROSS, R. E.: Experiences with surgical repair of atrial septal defects. J. Thoracic Surg. **30:** 469, 1955.

[19] SELZER, A.: Defect of the ventricular septum. Summary of twelve cases and review of the literature. Arch. Int. Med. **84:** 798, 1949.

[20] —, AND LAQUEUR, G. L.: The Eisenmenger complex and its relation to the uncomplicated defect of the ventricular septum. Review of thirty-five autopsied cases of Eisenmenger's complex, including two new cases. Arch. Int. Med. **87:** 218, 1951.

[21] —: Defects of the cardiac septums. J.A.M.A. **154:** 129, 1954.

Medical Eponyms

By ROBERT W. BUCK, M.D.

Krönig's Isthmus. Dr. Georg Krönig (1856–1911). Docent in the University of Berlin, published his paper "On the Topography and Percussion of the Lung Apices" (*Zur Topographie der Lungenspitzen und ihrer Percussion*) in the *Berliner klinische Wochenschrift* 26: 809–812 (September 16) 1889.

"The examination of a patient who had been referred to me was the beginning of a series of determinations of the borders of the lung apices as well as the lung margins which I will briefly report here. After I had determined the anterior supraclavicular margin of the lung in the usual fashion, that is by gentle percussion, I proceeded, still percussing very lightly to the posterior aspect, and thereby obtained the following results: On the right side, as on the left, there appeared a line which extended medially in a wide arch with its convexity directed inward and which approached to within a centimeter of the midline, on the left at the level of a line between the second and third thoracic spines, on the right at the level of the fourth thoracic spine. In this case the right apex was diseased . . . while the left showed a normal condition. . . . Inasmuch as I had obviously been successful in determining not only the height of the lung apices but also their breadth . . . I tried to determine similarly the lateral margin. . . .The determination of the posterior lateral border is easy in many cases, especially in thin individuals, but is frequently difficult in powerfully built, extremely muscular, or fat persons. The lateral border which I have outlined on the anterior surface is extremely trustworthy. It runs from about the middle of the anterior margin of the trapezius muscle, curves down sharply, cuts the clavicle at about the line between its middle and outer third, and then courses outward diagonally to the axilla. From the configuration of these normal clinical margins, it will now be possible, without great difficulty, to hypothecate the necessary shift which will occur when there are pathological changes in the lung apices. Diseases which reduce the air content will shift the medial border outward and the lateral border inwards."

An Assessment of the Exercise Capacity of Cardiac Patients

By C. H. WYNDHAM, M.B., M.R.C.P. (LOND.) AND J. S. WARD, B.A.

An attempt is made to relate the level of exercise at which disability occurs in cardiac patients with known oxygen consumption figures for various tasks. The limit to the maximum level of exercise in some patients with rheumatic heart disease is set by circulatory parameters, as in normal subjects, in others it is set by the excessive ventilatory cost of exercise.

THE rehabilitation of the patient with heart disease must include placing him in appropriate employment. Gainful work serves not only economic ends but has important psychologic benefits. One of the important decisions the clinician must therefore make is an assessment of the level of effort that the patient can safely undertake in employment and sport. Traditionally the evaluation is made on subjective symptoms and physical signs. With reliance chiefly on the patient's statement of the grade of effort that produces breathlessness and discomfort the physician places him in one of the categories of functional capacity outlined by the New York Heart Association.

The clinical assessment has obvious limitations. The main weakness is apparent when one attempts to relate the level of effort at which the patient claims that disability occurs to a physiologic measure of work, namely, liters of oxygen consumed per minute. Unless this is done it is virtually impossible to match precisely an evaluation of the patient's functional capacity with the grade of effort required to carry out various types of work or sport. Some attempts have been made in this direction by Nylin[1] and Bruce and Rodgers[2] but the level of oxygen consumption at which disability occurs is not readily obtainable by their methods. The present studies are an endeavor to define precisely the maximum exercise capacities of cardiac patients in terms of liters of oxygen consumption per minute.

The maximum capacity for effort of normal men can be defined as the maximum level of "aerobic" oxygen consumption. Åstrand[3] and Taylor and associates[4] have demonstrated clearly that this is the rate of oxygen consumption at which a further increase in the grade of work does not call forth any addition to the level of oxygen consumption. It merely results in an increase in oxygen debt and a shortening of the time of effort. In the laboratory this figure is determined by exercising the subject at increasingly severe grades of work until a level of oxygen consumption, as defined above, is reached. The method is tedious and in sick patients severe grades of work must, of necessity, be avoided.

Recent observations by Berggren and Christensen[5] and Åstrand[3] suggested that the maximum aerobic oxygen capacity can be determined without imposing high work loads. It was shown in normal subjects that heart rate is a linear function of oxygen consumption up to the maximum level of aerobic oxygen consumption, and maximum heart rate of 194 $\pm$ 1.6 beats per minute is not exceeded in adults during severe exercise and that this rate is closely correlated with the maximum level of aerobic oxygen consumption. Hence if heart rate is plotted as a function of oxygen consumption at 3 or more grades of work and a linear curve is fitted to these plots and extrapolated to 190 beats per minute, then the oxygen consumption at this heart rate should closely approximate the maximum level of aerobic oxygen consumption of the individual measured by the more laborious method. Moreover, the 3 grades of work can be submaximal efforts.

Our first aim, therefore, has been to test the observations from Christensen's laboratory. Studies were made on 4 normal, trained men to satisfy ourselves as to the linearity of this

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functional relationship up to maximal effort, to establish whether the maximum heart rate of the individual correlated closely with the maximum aerobic oxygen capacity, and to determine the variability of oxygen consumption determined in this way.

Having satisfied ourselves on these 3 points, we then measured heart rate, oxygen consumption, and ventilation at 3 grades of work on a group of untrained normal subjects and on 10 ambulant patients with rheumatic heart disease. Particular attention in this study has been paid to the ventilatory volume per minute at different levels of exercise. This is because we and others[3, 5, 6] have shown that the maximum voluntary breathing capacity in normal individuals always exceeds by a good percentage the minute ventilatory volume observed at the maximum possible level of exercise. On this ground it is concluded that circulatory rather than ventilatory factors set the limit to the maximum level of oxygen consumption of normal individuals. In patients with rheumatic heart disease, however, Stock and Kennedy,[7] Richards and Dickinson,[8] and Cotes[9] have shown a variable decrease in maximum breathing capacity and an increase in the ventilatory cost of one particular grade of exercise. It is unfortunate that these investigators studied only one level of exercise because no light was shed on the probability of the ventilatory cost increasing in a rapidly nonlinear manner as the level of exercise is raised. Should this happen in cardiac patients the limit to the maximum level of oxygen consumption might well be imposed by ventilatory and not cardiac factors as in the normal individual. To test this possibility we have compared the ventilatory function of the cardiac patients during exercise with the normal range of ventilatory volume per minute at different levels of oxygen consumption, up to 1.5 L. of oxygen per minute, of 24 young men living at Johannesburg (altitude 6,000 feet above sea level).

Methods

Repeated determinations were made on the 4 trained African men at different levels of work both on stepping stools and on a bicycle ergometer. On the latter, maximal effort was studied. The second group of subjects consisted of members of the laboratory staff; some played games regularly, others were quite sedentary. The third group was that of the cardiac patients. They were all ambulatory and, except for cases 11, 12, 15, and 18, did not complain of breathlessness on exertion. The fourth group consisted of 24 untrained young African recruits to the gold mines.

All submaximal effort studies were made by the subjects stepping on and off a stool 1 foot in height. Work was continuous and rigidly standardized by means of a metronome. There were 3 work periods, each of 20 to 30 minutes' duration. The rates of stepping were 1/20 seconds, 1/10 seconds, 1/5 seconds, and 1/2½ seconds. Most cardiac patients were not put to the highest grade of stepping and cardiac cases 15 and 18 were unable to perform adequately at the third rate of work. Oxygen consumptions were measured by collecting expired air over 3 minutes, midway during the work period, in a Douglas bag or metering it directly into a Kofranyi-Michaelis apparatus. Aliquot samples were analyzed in a Haldane apparatus. Samples were required to check to at least 0.05 volumes per cent. Ventilation volume during work was taken from the 3-minute collection of expired air and expressed at body temperature, atmospheric pressure, and saturated air (B.T.P.S.). Maximum breathing capacities (M.B.C.) were determined over 15 seconds, the expired air being breathed into a Douglas bag. M.B.C.'s were repeated until 2 determinations checked closely. Heart rates were counted at the apex of the heart by auscultation, except in the cases of the men with fibrillation and the 4 normal men at the high rates of work. In those instances the rates are a mean of at least 5 estimations of ventricular rate from an electrocardiogram.

Results

Heart Rate as a Function of Oxygen Consumption

Our observations on 4 trained men at various grades of work up to maximal effort on a bicycle ergometer have demonstrated conclusively that heart rate is a truly linear function of oxygen consumption, and that the oxygen consumption at the maximum heart rates correlates closely with the maximum aerobic levels determined by successive increments in the rate of work.[10] At a given rate of work the standard deviation of individual oxygen consumption is 0.11 L. per minute, so that differences between observed oxygen consumptions that indicate a real difference (with 95 per cent confidence) are

$$0.11 \times \sqrt{2} \times 1.96 = 0.31 \text{ L. per minute}$$

Differences of this order in maximum aerobic oxygen consumptions are therefore also significant.

Linear curves were fitted to the plots of heart rate as a function of oxygen consumption at the 3 grades of submaximal work and were extrapolated to 190 heart beats per minute. The fitted curves for the cardiac men are given in figure 1 and for the cardiac women in figure 2. Comparisons between individuals of the maximum aerobic oxygen capacities obtained in this way are more meaningful when corrected to a standard weight. For this purpose we have arbitrarily selected 150 lbs. The corrected mean value of maximum aerobic oxygen consumption for the 4 trained men is 3.6 (range 2.8 to 5.0) L. of oxygen per minute; for the 5 laboratory staff men the mean is 3.4 (range 2.7 to 3.7) L. of oxygen per minute; for Åstrand's[3] athletic young men 4.0 L. of oxygen per minute; and for his athletic young women, 3.2 L. of oxygen per minute.

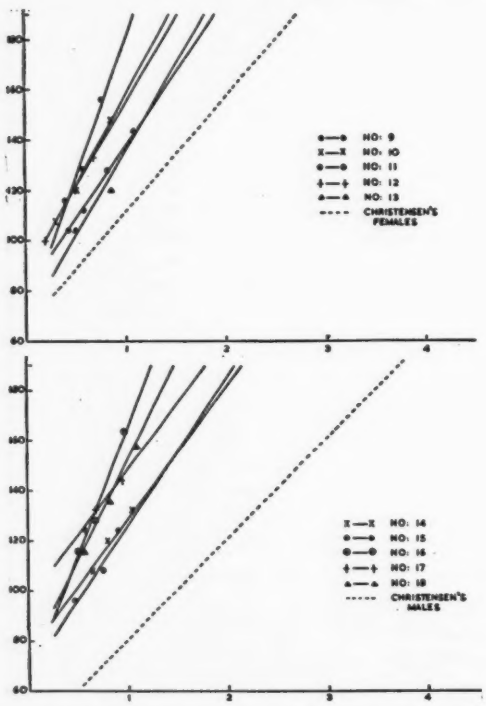

FIG. 1 *Top.* The curves fitted to heart rates at 3 submaximal rates of oxygen consumption (L. per minute, *abscissa*) for 5 cardiac women and extrapolated to 190 beats per minute (*ordinate*).

FIG. 2 *Bottom.* The curves fitted to heart rates (*ordinate*) at 3 rates of oxygen consumption (*abscissa*) for 5 cardiac men.

The maximum aerobic capacities of the cardiac patients derived from figures 1 and 2 are considered here as percentages of Åstrand's normal athletic young men and women. This is done to bring out more clearly the departure from normality of the cardiac patients. Two of the cardiac women have approximately 50 per cent of the normal maximum aerobic oxygen capacity and the remainder were within 75 per cent of normal. Two cardiac men, cases 16 and 18, have only 25 per cent of normal. The remainder were more than 50 per cent of normal. All of the cardiac patients fall outside the range of ± 2 S.D. from Åstrand's means.[3]

Two cardiac patients, 15 and 18, are instructive in that they demonstrate a limitation of effort due to ventilatory disability at a level of oxygen consumption well below that assessed from a heart rate of 190 beats per minute as the maximum. In other words, they are limited by ventilatory and not circulatory factors as is the case in normal men and in the other 8 cardiac patients. Case 18, table 1, on June 7, was fibrillating at 100 to 120 beats per minute at rest, and at a stepping rate of 1 step/10 seconds and an oxygen consumption of 0.79 L. of oxygen per minute he had a heart rate of 190 beats per minute. He was very breathless and was unable to perform at 1 step/5 seconds for sufficiently long to measure oxygen consumption. He was acutely distressed but his heart rate did not rise above 190 beats per minute. By July 6 he had been established in regular rhythm on quinidine. He was then able to do 1 step/5 seconds for 10 minutes even though very breathless at a heart rate of 158 beats per minute. The oxygen consumption of 1.1 L. per minute at 1 step/5 seconds is the maximum level of effort, rather than 1.5 L. of oxygen per minute obtained from extrapolation of heart rate to 190 beats per minute.

Similarly, case 15 was very breathless at 1 step/5 seconds at an oxygen consumption of 0.89 L. per minute with a heart rate of 124 beats per minute. This figure is his maximum level of oxygen consumption rather than 2.2 L.

TABLE 1.—*Exercise Capacity Tests on Subject No. 18**

Date	Rate of work	Heart rate				Ventilation rate (B.T.P.S.) (L./min.)	Oxygen cons. (L./min.)	Oxygen per cent absorbed	Clinical state
		5 min.	10 min.	15 min.	20 min.				
7/6/55	Mild	132	142	145	131	32.3	0.596	2.52	Performed with slight dyspnea
6/7/55	Mild	110	115	116	116	24.7	0.542	3.38	Performed with ease
7/6/55	Moderate	141	170	180	180	45.1	0.789	2.40	Dyspneic, tightness across chest
6/7/55	Moderate	128	136	138	132	33.6	0.812	3.31	Somewhat dyspneic
7/6/55	Moderately hard	180	—	—	—	—	—	—	Unable to do more than 5 minutes; marked dyspnea and weakness of knee joints
6/7/55	Moderately hard	153	158	—	—	70.0	1.089	2.52	Very dyspneic after 4 minutes; weakness in knees

* The first observations were made on June 7, 1955, when no. 18 was in atrial fibrillation, and again on July 6, 1955, when he was in regular rhythm.

of oxygen per minute obtained by extrapolating heart rate to 190 beats per minute. Case 15 was fibrillating, but the rate was well controlled on digitalis. He had been in cardiac failure previously and now had ascites and edema, which was treated by weekly injections of mercurial diuretics.

Ventilation-Volume (B.T.P.) as a Function of Oxygen Consumption

The ventilation volume per minute as a function of oxygen consumption of our 24 men at 6,000 feet altitude can be compared with Åstrand's observations on 40 young men at sea level. At 1 L. of oxygen consumption per minute the mean ventilation of our men is 29.3 ± 0.5 L. per minute, which is significantly different from Åstrand's 20.6 ± 0.5 at sea level. The difference of 45 per cent is undoubtedly due to the effect of altitude.

In figure 3 are given the ventilatory volumes of the 24 men at rest and at 3 rates of work. Tolerance limits have been calculated that include almost all observations in the experimental population,* hence any curves of ventilation that fall outside these tolerance limits can be regarded as abnormal. All of the laboratory staff and the 4 trained men fall within the limits. With 2 exceptions the cardiac patients also fall within the limits. Two features characterize the responses of the exceptions, no. 15 and 18. First, ventilation was greatly in excess of normal, even at low levels of oxygen consumption and second, the minute ventilation increased in a markedly nonlinear fashion with rise in oxygen consumption.

Both no. 18 and 15 were slightly breathless at the lowest level of work and more breathless at the intermediate level; and no. 18, in his first session, could not do the highest level, but was able to carry on for 10 minutes, although very breathless, on the second occasion when regular rhythm was established. Both of these men had markedly diminished M.B.C.'s and

* The problem is to set limits within which we expect subjects for the same population to fall.

A tolerance region will be set for $\hat{\alpha}$ and $\hat{\beta}$ in combination by using the fact that

$$\Gamma_{11}(\hat{\alpha} - A)^2 + 2\Gamma_{12}(\hat{\alpha} - A)(\hat{\beta} - B) + \Gamma_{22}(\hat{\beta} - B)^2$$

is a χ^2_2 variable if the joint distribution of $\hat{\alpha}$ and $\hat{\beta}$ is normal and Γ_{ij} are the coefficients of the inverse of the covariance matrix of $\hat{\alpha}$ and $\hat{\beta}$. The tolerance region is defined by an ellipse

$$\hat{\Gamma}_{11}(\hat{\alpha} - \hat{A})^2 + 2\hat{\Gamma}_{12}(\hat{\alpha} - \hat{A})(\hat{\beta} - \hat{B}) + \hat{\Gamma}_{22}(\hat{\beta} - \hat{B})^2 = C(\Theta_1\Theta_2 k)$$

where C is a constant (depending on the sample size k) such that we may state with 100 Θ_2 per cent confidence that this ellipse contains at least 100 Θ_1 per cent of the population of $(\hat{\alpha}, \hat{\beta})$ pairs. As $k \to \infty$, $C \to \chi^2_2$ (Θ_1). This ellipse having been defined, 2 bands may be calculated that are the tolerance limits to the individual straight lines $0 = \hat{\alpha} + \hat{\beta}V$. This is done by finding the minimum and maximum of $\hat{\alpha} + \hat{\beta}V$ subject to the condition that $(\hat{\alpha}, \hat{\beta})$ lies on the ellipse given above.

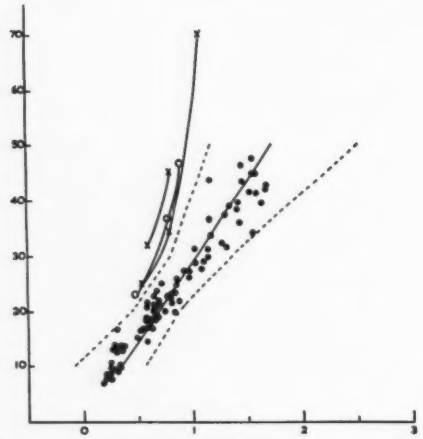

FIG. 3. Ventilation, liters per minute B.T.P.S. (*ordinate*), as a function of oxygen consumption at rest (*abscissa*) and at 3 rates of work of 24 healthy young men with the tolerance limits. ×———× is the data of cardiac no. 18. ○———○ is the data of cardiac no. 15.

hence a small ventilatory reserve (*M.B.C. — ventilation per minute/M.B.C.*) at the high level of work.

Of the other cardiac patients among the women only no. 11 and 12 complained of breathlessness during the tests. No. 11 did so at a ventilatory rate of 25.0 L. per minute. Her M.B.C. was 101.4 L. per minute. Her ventilatory reserve was thus 75 per cent when breathlessness was observed. By contrast the 4 trained men were breathless only when more than 60 per cent of the ventilatory reserve was employed.

DISCUSSION

In normal men oxygen consumption increases linearly with rate of work up to a maximum value designated the maximum "aerobic" oxygen consumption. Further increase in rate of work does not produce any rise in oxygen consumption. Ventilation volume per minute at the maximum level of oxygen consumption is less than the maximum voluntary breathing capacity, hence one can infer that even though these subjects are breathless at this level of effort, nonetheless there is adequate ventilatory reserve. This being the case, the limit to the rate of oxygen consumption per minute in

TABLE 2.—*Experimental Observations on Subjects*

Subject no.	Mean heart rate (beats/min.)	Oxygen consumption (L./min.)	Ventilation B.T.P.S. (L./min.)	M.B.C. (L./min.)
Laboratory Staff				
5	108	0.73	31.37	163.0
	116	1.01	30.83	
	148	1.64	48.22	
6	96	0.69	23.02	86.3
	112	1.06	31.51	
	132	1.57	44.66	
7	84	0.60	18.91	142.5
	96	0.86	28.77	
	124	1.64	44.94	
8 (unfit)	92	0.71	22.19	189.1
	108	1.16	32.61	
	132	1.68	42.20	
8 (fit)	80	0.84	20.00	
	90	1.16	27.54	
	120	1.84	43.16	
	148	2.72	63.43	
	188	3.48	99.87	
Women Cardiacs				
9	116	0.41	13.97	142.5
	128	0.57	18.08	
	156	0.76	25.03	
10	108	0.31	10.28	74.0
	120	0.51	19.45	
	148	0.84	26.85	
11	104	0.43	15.76	101.4
	112	0.58	21.65	
	128	0.83	25.03	
12	100	0.19	7.81	95.9
	108	0.30	11.51	
	132	0.67	25.76	
13	104	0.50	14.66	98.6
	120	0.84	23.43	
	144	1.09	29.59	
Men Cardiacs				
14	108	0.65	19.73	178.1
	120	0.80	23.43	
	132	1.07	30.14	
15	96	0.47	22.61	76.7
	112	0.77	35.60	
	124	0.89	46.60	
16	116	0.50	16.99	153.4
	128	0.67	20.55	
	164	0.97	30.37	
17	124	0.57	18.77	86.3
	132	0.67	21.78	
	144	0.96	30.33	
18*				

* See table 1.

maximal exercise is set by circulatory and not ventilatory factors.

The circulatory parameters concerned in the rate at which the body utilizes oxygen, aerobically, during exercise are heart rate, stroke volume and arteriovenous oxygen difference. The relationship may be expressed as follows:

$$\begin{matrix}\text{O}_2 \text{ consumption} \\ \text{(L. per minute)}\end{matrix} = \begin{matrix}\text{Heart rate} \\ \text{(beats per minute)}\end{matrix} \times \begin{matrix}\text{Stroke volume} \\ \text{(ml. per minute)}\end{matrix} \times \begin{matrix}\text{A-V difference} \\ \text{(ml. per 100 ml. blood)}\end{matrix}$$

The interrelationship of these variables at different rates of oxygen consumption is contained in the data obtained by the direct Fick determinations of Donald and associates[11, 12] Dexter and associates,[13, 14] and Freedman and associates,[15] on normal and cardiac volunteers. Direct Fick studies were made at a maximum work rate of 2.0 L. oxygen per minute. Recently Asmussen and Nielsen[16] obtained data at or near the maximum working capacity using the uptake of an inert gas and a dye-dilution technic. From these various studies it is now possible to make a relatively coherent statement on the way in which the 3 circulatory parameters contribute to an increase in oxygen consumption.

In both Nielsen's and Freedman's studies stroke volume increases with rise in oxygen consumption up to a maximum, which occurs at an oxygen consumption of between 1.4 and 1.6 L. per minute. Heart rate and A-V difference, on the other hand, both increase linearly with rise in oxygen consumption right up to the maximum aerobic oxygen consumption. At this level of oxygen consumption, heart rate in normal adults reaches a limiting value of 190 beats per minute.[3] The limiting value of A-V difference is not known so precisely. Even at high levels of cardiac output during exercise a percentage of the total outflow goes to areas such as brain and liver where the extraction rate of oxygen is low. The figure usually given for maximum A-V difference of 140–150 ml. per L. of blood therefore seems reasonable. The actual value will undoubtedly depend upon the volume of muscle engaged in exercise.[4] From these data it can be concluded that, at low levels of effort in normal men, stroke volume, heart rate and A-V difference all contribute to the rate at which oxygen is made available to tissues. Above a level of 1.5 L. of oxygen per minute (approximately 6 times the resting level) only heart rate and A-V difference are involved. Both increase as linear functions of oxygen consumption up to the maximum aerobic level.

The situation with cardiac patients is not so simple. In 8 of the 10 cases studied by us ventilation volume per minute as a function of oxygen consumption fell within the tolerance limits we have calculated for normal men. Moreover, the ventilation rate that would obtain at the maximum aerobic oxygen consumption (obtained by extrapolation of heart rate to 190 beats per minute) was less than the maximum breathing capacity. These cases, therefore, in these 2 respects conformed to normal. Two cardiac patients were, however, quite different. Even at the low rate of work they were breathless and ventilation was greater than normal. At high rates of work they were very breathless and ventilation as a function of oxygen consumption rose nonlinearly, so that no. 18, at an oxygen consumption of 1.0 L. per minute, ventilated at twice the normal volume. The maximum breathing capacities of these men were well below normal. Ventilation at the highest rates of work encroached seriously, therefore, upon ventilatory reserve. Heart rates of the 2 men, no. 15 and 18, were well below 190 beats per minute when they were very breathless. It is probably safe to say that in these 2 men the factor that limits exercise is primarily respiratory and not cardiac capacity per se. An objective method of determining the upper permissible limit of effort would be the level of oxygen consumption at which breathlessness produced discomfort. For no. 15 and 18 this would be 0.89 and 0.79 L. of oxygen per minute respectively. An alternative would be the point in the ventilation curve where it tends to become highly nonlinear. The minute volume ventilated by these 2 cardiac cases is grossly in excess of normal and raises an interesting problem in the control of ventilation. The explanation is unlikely to be a rise in pCO_2 in blood because the percentage of CO_2 in expired air is well below normal, indi-

cating that CO_2 is being blown off as in voluntary hyperventilation. There are 2 probable explanations. One is an accumulation of edema in pulmonary tissues with a loss of lung elasticity. Hayward and Knott[17] have shown this condition in rheumatic heart patients with dyspnea. The other is the excessive accumulation of lactic acid in blood and has been demonstrated by Cotes.[9] Both mechanisms are undoubtedly due to an inability to raise the cardiac output in a normal manner with increase in exercise. Hence it can probably safely be inferred in these and similar patients that the level of oxygen consumption at which ventilation departs in a markedly nonlinear manner from the normal is the level of effort at which cardiac output also fails to show the normal response to exercise.

In the other 8 cardiac cases the factor limiting exercise was not ventilatory function, as pointed out. Can we assume that the heart rate of 190 beats per minute was correlated, as in normal subjects, with the maximum aerobic oxygen capacity? The question can be put in another way that clarifies the issue. Is there any evidence in cardiac patients that at a heart rate of 190 beats per minute either A-V difference or stroke volume have not been employed up to their limits? If they have, then clearly at a heart rate of 190 beats per minute there is no other way of transporting more oxygen by the circulation and 190 beats per minute must be correlated with the maximum aerobic oxygen capacity. Dexter's data[13, 14] throw light on this problem if stroke volume, A-V difference, and heart rates are plotted as functions of oxygen consumption. The main difference from normal is that severe cardiac cases are unable to increase stroke volume with increase in effort. Consequently heart rate and A-V difference as function of oxygen consumption rise more rapidly than in normal subjects and reach their limiting values at relatively low levels of oxygen consumption. In both severe and mild cardiac cases extrapolation of A-V difference to 140 to 150 ml. per L. of blood indicates that this level is reached at lower levels of oxygen consumption than is the heart rate of 190 beats per minute. We have shown that heart rate is a linear function of oxygen consumption and therefore can safely be extrapolated. The only question open to challenge is extrapolating A-V difference linearly. In the cardiac patient increase in cardiac output is limited because of the restriction in stroke volume. Consequently, as oxygen consumption increases, A-V difference is used up more rapidly, as is clear in Dexter's data, and not less rapidly than normal. The error, if any, in extrapolation of A-V difference will therefore be on the right side, viz., towards oxygen consumptions at 140 to 150 ml. per L. of blood, which are too low. Hence we can safely assume that at a heart rate of 190 beats per minute the other 2 parameters have been fully employed and therefore this heart rate must be closely correlated with the maximum aerobic oxygen capacity.

The majority of cardiac cases in this group did not complain of dyspnea during the tests, but 2 women did so complain. For example, no. 11 had a ventilation rate of 25.0 L. at 0.83 L. of oxygen per minute. Her maximum breathing capacity was 101.0 L. per minute. In spite of a ventilatory reserve of 75 per cent she complained of dyspnea. She was excessively worried about her "heart trouble" and had avoided any but the mildest form of exercise. Her musculature was flabby. Dyspnea could well have been due to a level of ventilation to which she was unaccustomed. There appears to be no cogent reason why such a patient should not lead a more active life. The clinician's impression was one of cardiac neurosis and our data are helpful in lending him confidence to encourage her to pursue a more active life with a limit set by her maximum oxygen consumption as in the other cardiac patients of this group.

In assessing the level of exercise and, more especially, the grade of work that the cardiac can be allowed to do, these 2 broad categories are useful. The cases with a ventilatory limitation should not be called upon to work for a normal day at a rate that produces more than mild breathlessness. The level of oxygen consumption at which mild and moderate breathlessness occurs is clearly apparent in the data on no. 15 and 18.

The cardiac patient with exercise capacity

limited by circulatory rather than ventilatory parameters is at present in greater danger of being misplaced in regard to the grade of work that is permissible. The criterion generally employed by the clinician for all cardiac patients is the level of work at which breathlessness occurs. In this group of patients, heart rate rises abnormally rapidly with increase in oxygen consumption and the circulatory parameters are exhausted at a level of ventilation that, as in normal subjects, is well below the maximum voluntary breathing capacity. Hence the maximum permissible effort of these cardiac patients must be judged in relation to the maximum aerobic oxygen capacity, as in normal men, rather than by the level of effort at which breathlessness occurs.

The maximum aerobic oxygen capacity defines the level of work that normal and trained men can sustain for only a few minutes before fatigue supervenes. It serves to differentiate between men with different capacities for maximum effort. Thus Åstrand[18] showed that Landy, the 4-minute miler, has a maximum aerobic capacity of over 5.0 L. of oxygen per minute, whereas the average of his young, fit men was 3.9 L. of oxygen per minute.[3] Its usefulness in industrial employment is as a standard against which to assess a permissible level of oxygen consumption for 8 hours of work. Thus Åstrand[3] stated that healthy factory workers should not work at more than half their maximum capacity. While there is no evidence that a similar grade of effort relative to the maximum capacity would have any harmful effect on the cardiac patient, we suggest that, until we have evidence on the point, the maximum permissible level of work be set at one third of the maximum aerobic oxygen capacity for this particular group of cardiac patients. This information should be of use to the hospital social worker in rehabilitating the cardiac patient. The range of permissible work can be judged in regard to meaningful domestic activities and industrial tasks by correcting the maximum aerobic oxygen consumption to 150 lbs. weight, and comparing them with data in tables from laboratories engaged in such studies.[19, 20]

A further use of the maximum aerobic oxygen consumption figure, whether assessed by ventilatory or circulatory criteria, is as an objective measure of the effect of type of heart disease and the regimen of therapy on the exercise status of the patient. Thus no. 18 was fibrillating on the first occasion and had acute discomfort at 0.79 L. of oxygen per minute, but after treatment with quinidine to bring him into regular rhythm he was able to exercise briefly at 1.1 L. of oxygen per minute and his ventilation volume per minute improved considerably. It may be equally useful to judge objectively the effect of valvulotomy. Finally, it is an index with which to judge the progress of the disease with time. Regular examinations, say at yearly intervals, would give a measure of the improvement or deterioration of the cardiac patient.

Summary

Heart rate, oxygen consumption, and minute ventilation volume were measured at 3 grades of work on 4 trained men, 5 untrained men, and 10 ambulatory cardiac patients with rheumatic heart disease. Ventilation volume/minute at different levels of oxygen consumption were also measured on 24 young men to set up standards against which to judge abnormality at an altitude of 6,000 feet above sea level.

Eight of the cardiac patients had ventilatory volumes/minute at the 3 levels of oxygen consumption that were essentially the same as normal subjects and therefore ventilatory function, as in normal subjects, did not appear to be the factor that sets a limit to the maximum possible level of oxygen consumption during severe exercise. Hence, as in normal subjects, the maximum level of oxygen consumption was obtained by extrapolation to 190 beats/minute of the heart rates obtained at 3 submaximal grades of work when the heart rates are plotted as a function of oxygen consumption.

Two of the cardiac patients had an abnormal pattern of ventilatory response to exercise. Even at mild effort they had a larger minute volume than normal and this departed further from normal as the level of exercise was raised. The possible implications of this observation are discussed and the primary cause is considered to be an inability to increase the

cardiac output in a normal manner in relation to exercise.

The ventilatory responses to exercise, therefore, serve to distinguish 2 clear categories of rheumatic heart disease patients. The method of assessing the maximum possible level of oxygen consumption of patients in these 2 categories is discussed.

It is suggested that assessment of the individual cardiac patient's maximum level of oxygen consumption can be employed as an objective index in choosing a safe level of work in employment, in assessing the influence of therapy or surgery, and in following the course of the disease with time.

Acknowledgment

We are pleased to acknowledge the help and useful criticism of Dr. van Lingen and Dr. MacGregor of the Department of Medicine, University of the Witwatersrand. The work was done in the Department of Medicine with Professor Elliott's permission. Mr. J. S. Maritz did the statistical analyses.

Summario in Interlingua

Velocitate del corde, consumption de oxygeno, e ventilation per minuta esseva mesurate a 3 nivellos de exercitio in 4 homines accostumate a labor physic, 5 homines non assi accostumate, e 10 patientes cardiac ambulatori qui habeva morbo cardiac rheumatic. Le volumine ventilatori per minuta esseva etiam mesurate in 24 juvene homines normal con le objectivo de establir standards pro le judicamento de anormalitates a un altitude de circa 5800 m supra le nivello del mar.

Octo del patientes cardiac habeva, a omnele 3 nivellos de consumption de oxygeno, volumines ventilatori per minuta que esseva essentialmente identic con le valores in subjectos normal. Per consequente, le function ventilatori in iste casos, exactemente como in subjectos normal, non pareva representar le factor que impone le limite del plus alte nivello possibile de consumption de oxygeno in exercitios sever. Assi, como in subjectos normal, le nivello maximal del consumption de oxygeno poteva esser obtenite super le base del velocitates cardiac obtenite a tres grados submaximal de exercitio per extrapolation a 190 pulsos per minuta in graphicos monstrante le velocitates cardiac como function del consumption de oxygeno.

Duo del patientes cardiac habeva forma anormal del responsa ventilatori a exercitio. Mesmo sub le conditiones de leve grados de effortio illes habeva volumines per minuta que excedeva le norma, e le differentias al le norma cresceva quando le nivello del exercitio esseva elevate. Le signification de iste factos es discutite, e le these es formulate que le causa primari es le incapacitate de augmentar le rendimento cardiac in relation normal al grado del exercitio.

Assi le responsa ventilatori a exercitio pote servir a distinguer clarmente duo categorias de patientes de morbo cardiac rheumatic. Es discutite le methodo de evalutar le plus alte nivello possibile del consumption de oxygeno del parte de patientes in iste duo categorias.

Es presentate le idea que le calculation del nivello maximal de consumption de oxygeno in le casos individual de patientes cardiac pote esser usate como indice objective in determinar qual nivello de effortio es admissibile in le occupation professional del patiente, in evalutar le influentia de therapia o chirurgia, e in traciar le disveloppamento del morbo in le curso del tempore.

REFERENCES

[1] Nylin, G.: More recent developments in heart-function tests. J.A.M.A. **109:** 1333, 1937.

[2] Bruce, R. A., and Rodgers, D. L.: Exercise tolerance and mitral stenosis. Am. J. Med. **15:** 35, 1953.

[3] Åstrand, P.: Experimental Studies of Physical Working Capacity in Relation to Sex and Age. Copenhagen, Munksgaard, 1952.

[4] Taylor, H. L., Buskirk, E., and Henschel, A.: Oxygen uptake and cardio-respiratory performance. J. Appl. Physiol. **8:** 73, 1955.

[5] Berggren, G., and Christensen, E. A.: Heart-rate and body temperature às indices of metabolic rate during work. Arbeitsphysiologie **14:** 255, 1950.

[6] Bock, A. V., and Dill, D. B.: The Physiology of Muscular Exercise. London, Longmans, Green, 1931.

[7] Stock, J. P., and Kennedy, M. C.: The quantitative assessment of disability in mitral stenosis. Lancet **265:** 5, 1953.

[9] RICHARDS, W., AND DICKINSON, JR.: Nature of cardiac and pulmonary dyspnea. Circulation **7:** 15, 1953.

[10] COTES, J. E.: Exercise ventilation in mitral stenosis. Clin. Sc. **14:** 317, 1955.

[11] WYNDHAM, C. H., STRYDOM, N. B., MORRISON, J. F., PETER, J., AND POTGIETER, Z. U.: Exercise capacity studies. In preparation.

[12] DONALD, K. W., BISHOP, J. M., CUMMINGS, G., AND WADE, O. L.: The effect of exercise on the cardiac output and circulatory dynamics of normal subjects. Clin. Sc. **14:** 37, 1955.

[13] —, AND WADE, O. L.: A study of circulatory dynamics during exercise in rheumatic heart disease. J. Clin. Invest. **33:** 1146, 1954.

[14] DEXTER, L., WHITTENBERGER, J. L., HAYNES F. W., GOODALE, W. T., GORLIN, R., AND SAWYER, C. G.: The effect of exercise on circulatory dynamics of normal individuals. J. Appl. Physiol. **3:** 439, 1951.

[15] GORLIN, R., SAWYER, C. G., HAYNES, F. W., GOODALE, W. T., AND DEXTER, L.: The effects of exercise on the circulatory dynamics in mitral stenosis. Am. Heart J. **41:** 192, 1951.

[16] FREEDMAN, M. E., SNIDER, G. L., BROSTOFF, P., KIMELBLOT, S., AND KATZ, L. N.: Training and exercise cardiac output. J. Appl. Physiol. **8:** 37, 1955.

[17] ASMUSSEN, E., AND NIELSEN, M.: Cardiac output in rest and work determined simultaneously by the acetylene and dye injection methods. Acta physiol. scandinav. **27:** 217, 1952.

[18] HAYWARD, G. W., AND KNOTT, J. M.: The effect of exercise on lung distensibility and respiratory work in mitral stenosis. Brit. Heart J. **17:** 303, 1955.

[19] ÅSTRAND, P.: New records in human power. Nature **176:** 922, 1955.

[20] DROESE, W., KOFRANYI, E., KRAUT, H., AND WILDEMANN, L.: Investigations regarding the energy expenditure of housewives. Arbeitsphysiologie **14:** 63, 1949.

[21] PASSMORE, R., AND DURNIN, J. V.: Human energy expenditure. Physiol. Rev. **35:** 801, 1955.

Harris, P., Fritts, H. W., Jr., Clauss, R. H., Odell, J. E., and Cournand, A.: Influence of Acetylcholine on Human Pulmonary Circulation under Normal and Hypoxic Conditions. Proc. Soc. Exper. Biol. & Med. **93:** 77 (Oct.), 1956.

Acetylcholine infused into the main pulmonary artery caused a slight fall in pulmonary arterial pressure when the subject breathed ambient air, but a greater fall in pressure after pulmonary hypertension had been produced by hypoxia. The fall in pressure was associated with either a constant or an increased cardiac output. The evidence suggested that acetylcholine caused vasodilatation in the human lungs. This observation is in conflict with earlier reports of others that acetylcholine can constrict vessels of animal lungs.

AVIADO

The Problem of Bioassay and Comparative Potency of Diuretics

II. Carbonic Anhydrase Inhibitors as Oral Diuretics

By RALPH V. FORD, M.D., CHARLES L. SPURR, M.D., AND JOHN H. MOYER, M.D.

Oral diuretic agents are widely used with but little information concerning their relative diuretic and toxic effects. A method is reported here for the bioassay of oral diuretic agents so that their comparative potency may be established. Four carbonic anhydrase inhibitors are compared by this method.

AS THE uses for diuretic agents have multiplied because of a greater understanding of the pathologic physiology of salt and water metabolism, a fertile field for the development of new agents that will increase the excretion of sodium and water has developed. Diuretics may be categorized according to their mechanisms of action.[1] The most commonly used diuretic agents are, of course, the organomercurials and these are available for parenteral injection as well as oral use. The parenteral forms are used in markedly edematous states and the oral mercurials find wide usefulness for maintenance therapy. The mechanism of action of the mercurial compounds has been reported to be the inhibition of succinic dehydrogenase activity in Henle's loop of the nephron.[2] Second only in importance to the mercurial diuretics are the agents that promote the excretion of sodium and water by the inhibition of carbonic anhydrase activity in the distal convoluted tubule of the nephron.[3] In general, these are sulfonamide derivatives that may be administered orally to assist the control of mild edema.

The purpose of the present study is to report the method for the bioassay of carbonic anhydrase inhibitors as diuretic agents with the result that the comparative potency of these agents may be established. The 4 drugs to be compared are all sulfonamide derivatives and include acetazoleamide (Diamox),* 6-ethoxybenzothiazole-2-sulfonamide (U-4191),† Butamide (SKF-4965)‡ and P-carboxybenzene sulfonamide (Dirnate)§ (fig. 1).

MATERIALS AND METHODS

This bioassay was conducted on a metabolic ward, utilizing men with mild heart failure who had previously demonstrated evidence of edema but, who, at the time of the study, were relatively edema-free. Each of 4 drugs was given to 10 patients and frequently the same patients received more than one of the drugs. The patients drank 3000 ml. of distilled water per 24 hours and ate a diet containing 50 mEq. of sodium per 24 hours. Twenty-four-hour urine specimens were analyzed for sodium, potassium, chloride, and volume. The patients were weighed each morning before breakfast and after voiding. After suitable control periods, the patient's urinary excretion rate of sodium was approximately 90 to 95 per cent of the dietary sodium intake. The patient's excretion rate for sodium continued at this constant level for at least 3 days. The patient was then given a single dose after breakfast of the drug to be tested on 2 consecutive days and the body weights and excretion rates of water and electrolytes were determined. After the drug was stopped the patient's excretion rate of sodium usually decreased for 1 to 3 days, during which time the body stores of sodium were replenished and the patient once more began to excrete at a fairly constant rate, which was very close to his dietary sodium intake. Thus, it was usually 7 days between the administration of the different drugs to each patient (fig. 2) as well as between the different dose levels employed for each drug.

Since the range between threshold dose and the maximum effective dose for increasing water and

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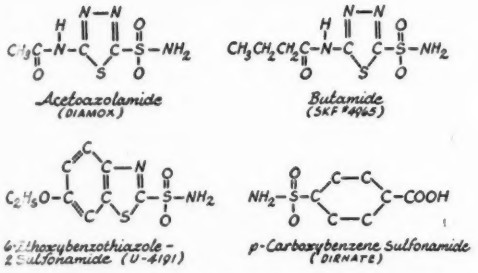

FIG. 1. Structural formulas for the test drugs emphasize their basic sulfonamide structure.

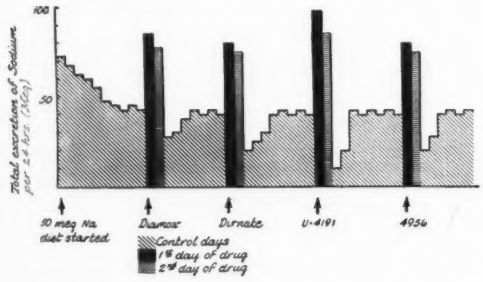

FIG. 2. The technic for studying these diuretic agents consists primarily of the observation of sodium excretion. The increases due to the various drugs are followed by 1- to 3-day periods of "compensation" during which sodium excretion is depressed.

electrolyte excretion with these drugs was so small, it was impossible to establish a good dose-response curve. However, in 3 of the 4 drugs tested, very small doses were administered in a log-dose incremental fashion until further increases in dosage resulted in no further increase in the excretion rate of sodium. This point was arbitrarily termed the apex of the curve. Figure 3 shows that with 1 of the experimental drugs studied (U-4191), there was a minor increase in the excretion rate for sodium at the small dose tested (33.75 mg.) followed by an increasing magnitude of response until the 125-mg. dose was reached, at which point the curve flattened out and became parallel to the base line.* This same procedure was used in the establishment of the apex point for Diamox and SKF-4965, but not for Dirnate. After this apex was established, a dose of at least 2 times that dose at the apex was administered as the testing dose for the particular drug (fig. 3). The apex point for each of 3 drugs was roughly similar except that SKF-4965 was slightly more potent.

* Although the curve as plotted shows a slightly greater increase at the 250-mg. dose point, this increase was shown to be not significant by statistical analysis.

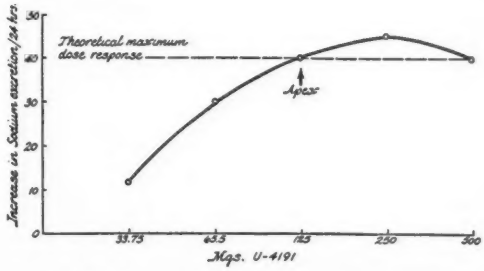

FIG. 3. The apex point is determined experimentally by progressive increases in the dose until no additional increase in sodium excretion is observed. The test dose is then twice this apex dose. Although the curve as plotted shows a slightly greater increase at the 250-mg. dose point, this was shown to be not significant by statistical analysis.

Thus, in the cases of Diamox and U-4191, the dosage for each test was 250 mg. daily. Experimental preparation SKF-4965 was tested at 150 mg., since its apex dose was 75 mg. In the case of Dirnate, the apex was not established, but, following the recommendations of the pharmaceutical pharmacologist, a dose of 2000 mg. was administered as a single dose.

RESULTS

The values are recorded as the increases in sodium, potassium, chloride, water and the decrease in weight as an average of the 2 consecutive days during which the comparative test dose (twice the maximum effective dose for each drug) was administered.

In table 1, the changes following the administration of Diamox in excretion rates of electrolytes and water as well as the changes in weight are recorded. There was an average increase in the urinary excretion of sodium per 24 hours of 35 mEq. ($p < .001$), which is the average of 2 consecutive 24 hours during which the drug was administered at a dosage of 250 mg. each day. The excretion rate for potassium increased by 35 mEq. per 24 hours ($p < .001$), while the chloride excretion rate decreased by 9 mEq. per 24 hours ($p < .01$). The rate of water excretion increased by 0.44 L. per 24 hours ($p < .001$) and the weight decreased by 0.3 Kg. per 24 hours ($p < .02$). The increase in the excretion rate of sodium per 24 hours was 31 mEq. for Dirnate, 44 mEq. for U-4191, and 31 mEq. for SKF-4965. Changes in the excretion rates of potassium, chloride, and water as

TABLE 1.—*Summary of the Average Effect on Body Weight and the Excretion Rates of Water and Electrolytes*

Drug	Increase in sodium excretion (mEq./24 hr.)	Increase in potassium excretion (mEq./24 hr.)	Change in chloride excretion (mEq./24 hr.)	Increase in water excretion (L./24 hr.)	Weight change (Kg.)
Diamox	35	35	−9	0.44	−0.3
Dirnate	31	28	−6	0.24	−0.2
U-4191	44	37	−6	0.43	−0.6
SKF-4965	31	43	−11	0.20	−0.2

well as the change in weight were roughly similar for these 3 drugs and the general pattern was similar to that of Diamox.

The significance of the data has been established by the analysis of variance. This indicates that there is no significant difference among the 4 drugs tested in their ability to augment the excretion rate of sodium, potassium, chloride, or water or to induce a change in weight. Application of Student's t test to the changes following each drug further shows that the increase for the excretion of sodium, potassium, and water are significant as well as the change in weight, but that the changes in chloride excretion are of borderline significance. An analysis of variance of previous experimental data has indicated that there is no significant difference between patients in their responses to the various drugs tested.[4]

DISCUSSION

The use of carbonic anhydrase inhibitors as oral diuretics has found distinct clinical application in the treatment of mild edema due to numerous causes. The mechanism of the diuretic effect is the inhibition of the carbonic anhydrase enzyme system at the level of the distal tubule in the kidney. This enzyme system is responsible for the exchange of intracellular hydrogen ions with the intratubular sodium, which results in acidification of the urine. Since sulfanilamide and certain of its derivatives are capable of inhibiting this enzyme system, there is a greater loss of sodium by way of the urine following their administration. It thus seemed reasonable to search for relatively nontoxic inhibitors of carbonic anhydrase. This search has yielded at least 4 compounds whose activity in this regard is adequate, yet they are not too toxic for oral administration (fig. 1).

Among the drugs tested, Diamox is the only one that is clinically available at this time. Dirnate is not now and probably will not become commercially available. U-4191, and Butamide have not been marketed for clinical use as yet, but probably will be at some future date.

The indications for the use of these drugs include maintenance therapy between parenteral mercurial injections for the treatment of severe congestive heart failure, the treatment of mild heart failure, premenstrual edema, the nephrotic syndrome (in the absence of acidosis), hepatic and nutritional edema, and occasionally in the control of the edema associated with steroid therapy. In the latter entity, so-called "steroid edema," the use of carbonic anhydrase inhibitors is somewhat limited because they produce a kaluresis, which may upset normal acid-base balance, since the primary therapy, namely steroids, also exert this same pharmacologic effect.

This wide usage for oral diuretics in general, and for carbonic anhydrase inhibitors specifically, necessitates a method whereby these drugs can be compared in terms of diuretic potency and the incidence and severity of side reactions. In previous studies,[4, 5] the technics for bioassay of mercurial diuretics have been described. It has been shown that the response to a diuretic agent is dependent upon the dietary sodium intake as well as the dose of the diuretic agent. These observations thus have established the necessity of maintaining a constant dietary intake of sodium when doing comparative diuretic bioassays. Since these drugs are relatively potent (as compared to carbonic anhydrase inhibitors), the changes in the excretion of electrolytes, water, and weight can be measured accurately and a dosage-response curve can be determined. By comparing dosage-response curves the potency estimation of the various diuretic agents can be determined.

In contrast to the mercurials, the potency of carbonic anhydrase inhibitors as natriuretic agents is comparatively small. Further, the

dose ranges of the carbonic anhydrase inhibitors that produce significant and increasing responses in the excretion of sodium and water are so narrow that the establishment of typical dose-response curves is practically impossible. Thus, it is necessary to determine the point at which a further increase in the dose of each of these drugs does not result in an additional increase in the excretion rate of water or electrolytes and a decrease in weight. Then, by using a dose greater than this apex (we have arbitrarily selected a dose 2 times that of the apex dose) and administering this dose a sufficient number of times to be statistically significant, one is able to compare the relative potency of the carbonic anhydrase inhibitors. This approach established the maximum response that can be obtained with the 4 compounds under study irrespective of the dose requirement. However, with one exception (Dirnate), the dosages of each drug that produced maximum diuresis and natriuresis were roughly similar. Dirnate was given at a much larger dose, but, since it is no longer available, it has been impossible for us to study the problem of determining the apex point of this drug. However, comparison of these drugs through an analysis of variance reveals no significant difference among them in their ability to influence the excretion rates of sodium and other electrolytes as well as water and weight change at the dosages administered. No adverse side effects were noted with these dosages.

It is of interest to compare an orally administered mercurial diuretic chlormerodrin (Neohydrin) to Diamox during continued administration of each compound, since continued daily diuretic therapy may be required for adequate treatment of patients suffering from severe sodium and water retention as in severe heart failure. In figure 4 it is seen that the changes resulting from the administration of oral Neohydrin increased with continued administration of the drug. However, the changes following the administration of Diamox illustrate that although on the first day the changes were roughly equal to that of Neohydrin in clinically tolerable doses there was a decreasing response to the continued administration of Diamox for 5 successive days. This difference has been explained as being due to the development of compensatory mechanisms against the systemic acidosis that results from the administration of Diamox continuously. The full explanation is not available but an important factor is the decreased filtered load of bicarbonate presented to the tubules. Under controlled metabolic conditions the administration of 30 mg. (3 tablets) of Neohydrin orally produces an acute (2-day period of daily administration) increase in sodium excretion that is equal to that following the administration of 250 mg. of Diamox.

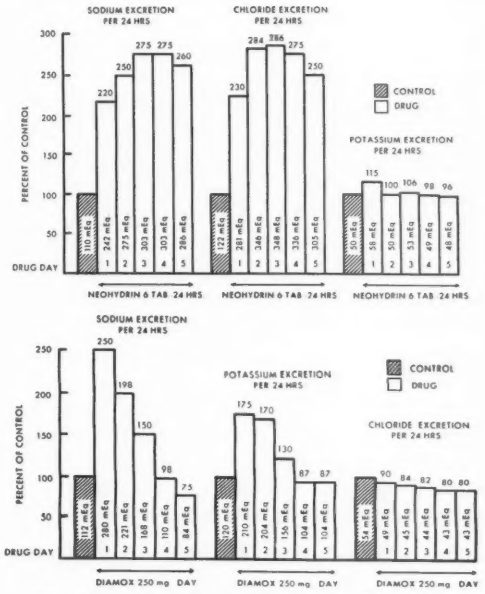

FIG. 4 *Top.* The oral administration of Neohydrin is followed by an increasing response on consecutive daily administration. *Bottom.* The oral administration of Diamox is followed by a decreasing response on consecutive daily administration.

SUMMARY

Utilization of controlled metabolic conditions, which furnish the patient with constant dietary and water intake, and measurement of electrolyte and water excretion, as well as weight change, permit determination of the comparative diuretic potency of orally administered carbonic anhydrase inhibitors.

No significant difference in maximum di-

uretic effect was found among 4 carbonic anhydrase inhibitors, Diamox, Dirnate, SKF-4965, and U-4191.

The acute response to the 4 carbonic anhydrase inhibitors was approximately equal to 3 tablets (30 mg.) of oral Neohydrin given as a single dose; but continued administration of Neohydrin on consecutive days resulted in an increase in the excretion rate of sodium, while the continued administration of Diamox as well as the other carbonic anhydrase inhibitors was accompanied by a declining rate of sodium excretion.

SUMMARIO IN INTERLINGUA

Sub conditiones metabolic regulate a provider le patiente de constante quantitates de natrium e aqua dietari, le mesuration del excretion de electrolytos e aqua insimul con determinationes de alterationes de peso permitte le evalutation comparative del potentia diuretic de oralmente administrate inhibitores de anhydrase carbonic.

Nulle significative differentias del potentia diuretic esseva trovate inter le 4 inhibitores de anhydrase carbonic: Diamox (acetazoleamido), Dirnato, SKF-4965, e U-4919.

Le responsa acute al 4 inhibitores de anhydrase carbonic esseva approximativemente equal a 3 tablettas (30 mg) de chlormerodrina oral (Neohydrina) administrate in un dose unic. Sed continue administrationes de Neohydrina con intervallos de un die resultava in un augmento del excretion de natrium, durante que le administration continue de Diamox e del altere inhibitores de anhydrase carbonic esseva accompaniate de un reduction del excretion de natrium.

REFERENCES

1 FORD, R. V., AND MOYER, J. H.: Diuretic therapy. Current concepts of the use of diuretics with emphasis on the methods of selection of the agent of choice. In press.

2 HANDLEY, C. A., AND LAVIK, P. S.: Inhibition of the kidney succinic dehydrogenase system by mercurial diuretics. J. Pharmacol. & Exper. Therap. **100:** 115, 1950.

3 MANN, T., AND KEILIN, D.: Sulphanilamide as specific inhibitor of carbonic anhydrase. Nature **146:** 164, 1940.

4 FORD, R. V., SPURR, C. L., AND MOYER, J. H.: The problem of bioassay and comparative potency of diuretics. I. Parenteral and oral mercurial diuretics. To be published.

5 —, —, —, AND HANDLEY, C. A.: Bioassay of diuretics. Fed. Proc. **14:** 340, 1955.

The application of the principles of science to the diagnosis and treatment of disease is only one limited aspect of medical practice. The practice of medicine in its broadest sense includes the whole relationship of the physician with his patient. It is an art, based to an increasing extent on the medical sciences, but comprising much that still remains outside the realm of any science. The art of medicine and the science of medicine are not antagonistic but supplementary to each other. There is no more contradiction between the science of medicine and the art of medicine than between the science of aeronautics and the art of flying.—FRANCIS W. PEABODY, 1881–1927.

Left Atrial Pressure Pulse in Mitral Valve Disease

A Correlation of Pressures Obtained by Transbronchial Puncture with the Valvular Lesion

By Andrew G. Morrow, M.D., F.A.C.S., Eugene Braunwald, M.D., J. Alex Haller, M.D., and Edward H. Sharp, M.D.

Left atrial pressures were determined by transbronchial puncture in 53 patients with mitral valve disease of proved type, and were analyzed by several methods. Two new methods of analysis, the rate of the *y* descent divided by the mean left atrial pressure, and the *y* descent for each 0.1-second interval divided by the mean left atrial pressure afforded the best separation of the patients with mitral insufficiency from those with mitral stenosis requiring a commissurotomy. In the presence of predominant mitral stenosis, however, the severity of accompanying mitral regurgitation could not be assessed.

IT HAS been well established that mitral valve disease and experimentally produced mitral valvular lesions alter the contour of the left atrial pressure pulse.[1-6] The purpose of this investigation was to evaluate the usefulness of several previously described[1-4] and 3 new methods of analysis of the left atrial pressure in distinguishing patients with predominant mitral insufficiency from those with predominant stenosis. This study is based on the preoperative left atrial pressure curves of 53 patients with mitral valve disease of proved type.

Material

Of the patients studied, 39 were found at operation to have significant mitral stenosis. In 32 of these patients there was either no palpable regurgitation or a minimal jet considered by the surgeon to be of little functional significance. Seven of the 39 patients with mitral stenosis were found to have, in addition, "significant" mitral insufficiency. This was evidenced by the presence of a regurgitant jet of moderate or severe intensity. The valve orifice in each of the 39 patients with mitral stenosis (including those with combined mitral stenosis and insufficiency) was less than 1 cm. in diameter and a commissurotomy was indicated and performed.

Fourteen patients had essentially pure mitral insufficiency. In 7 patients this diagnosis was established at operation or autopsy. The other 7 patients presented classic clinical, roentgenologic, and electrocardiographic findings of mitral insufficiency and at left heart catheterization were shown to have no diastolic gradient across the mitral valve.

From the Clinic of Surgery, National Heart Institute, National Institutes of Health, Bethesda, Md.

Methods

Left atrial pressures were determined preoperatively by transbronchial puncture as described by Allison and Linden[7] and Facquet and co-workers.[8] Local anesthesia was employed. Pressures were recorded through a no.-17 needle with a Statham P23A pressure-transducer employing either a Sanborn multi-channel recorder or a cathode-ray photographic recording system. There were no instances of hemorrhage, infection, or emphysema and the procedure was well tolerated even by severely ill patients. A detailed description of the technic of left heart pressure measurements by the transbronchial method forms the subject of a separate report.[9]

The components of the left atrial pressure pulse in a normal individual are illustrated in figure 1. The *a* wave is associated with atrial systole and follows the P wave of the electrocardiogram; the *z* point denotes the beginning of the second positive deflection, the *c* wave, associated with isometric ventricular contraction.[10] Atrial pressure then falls during the early portion of ventricular systole (*x* descent); it again rises to a third peak, the *v* wave, which occurs at the time of opening of the mitral valve. The decline in atrial pressure following the *v* point, designated as the *y* descent, is associated with rapid ventricular filling, i.e., it represents the so-called diastolic inflow phase.[11] The left atrial pressure then rises again in middiastole during the period of diastasis or slowed ventricular filling (designated as *D* in fig. 1) until the onset of the next atrial contraction.

In the nomenclature of Owen and Wood,[1] P_1 is the pressure at the peak of the *v* wave and P_2 is the pressure at the termination of the *y* descent. T_1 and T_2 are the corresponding points on the time scale. The pressures at the *z* point and at T_1 and T_2 were calculated in all patients. At least 4 complexes, usually covering a complete respiratory cycle, were

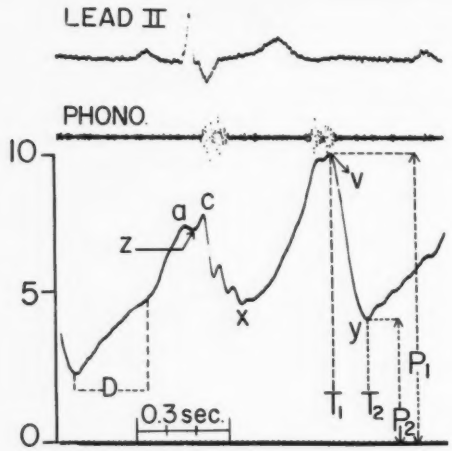

FIG. 1. The left atrial pressure pulse (mm. Hg) in a normal individual with sinus rhythm and right bundle-branch block.

analyzed in each tracing and average values were used in the final calculations. In patients with atrial fibrillation and a ventricular rate greater than 100, the 4 longest cardiac cycles were chosen for evaluation. Mean left atrial pressures were determined by planimetric integration.

RESULTS AND DISCUSSION

There was no significant difference between the average of the mean left atrial pressures of the 39 patients with mitral stenosis and the 14 patients with mitral insufficiency. However, obvious differences were found between the left atrial pressure tracings in mitral stenosis and pure mitral insufficiency. Figure 2*A* illustrates a typical curve from a patient with pure mitral stenosis and sinus rhythm. The *a-c* complexes and *v* waves are of similar amplitude, the "pulse pressure"* is narrow, the *y* descent is slow, the mean pressure is elevated, and diastasis is absent. Figure 2*B* is a tracing obtained from a patient with pure mitral insufficiency and sinus rhythm. The *v* wave rises far above the *a-c* complex and the *y* descent is rapid. The "pulse pressure" is wide, the mean pressure is elevated, and diastasis is present.

* The term "pulse pressure" is used in this report to denote the pressure difference between the highest and lowest points of the left atrial pulse wave. It is usually represented by the difference between the pressure at the peak of the *v* wave and that at the termination of the *y* descent.

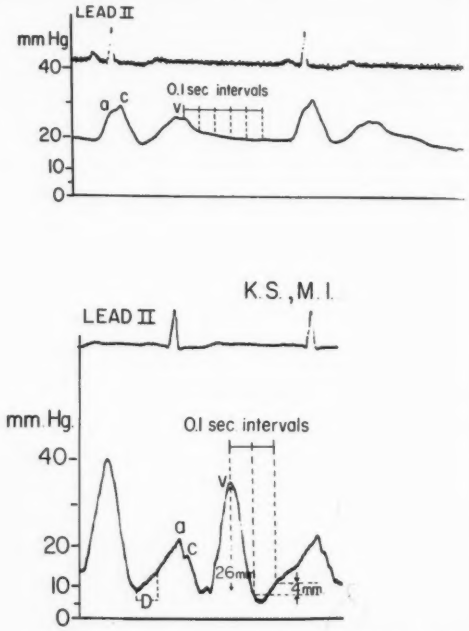

FIG. 2. *A. Top.* The left atrial pressure pulse in a patient with pure mitral stenosis and sinus rhythm. Note in particular the slow and prolonged *y* descent following the *v* wave. Diastasis is absent. *B. Bottom.* The left atrial pressure pulse in a patient with pure mitral insufficiency and sinus rhythm. The *y* descent is rapid and brief and diastasis (*D*) is evident.

Methods for quantification of the differences in the left atrial pressure curves associated with mitral stenosis and mitral insufficiency have been described by several authors [1-4] and the data from the present series were first analyzed according to their criteria. In figures 3, 4, and 6 the appropriate mathematical ratio is plotted along the abscissa. Each open circle represents a patient with sinus rhythm and each solid circle a patient with atrial fibrillation. Half circles designate those patients with mitral stenosis and significant mitral insufficiency.

Facquet and co-workers[2] considered the *v* wave in terms of its "pulse pressure" and diastolic pressure. In the terminology of figure 1 this may be expressed by the ratio $\frac{P_1 - P_2}{P_2}$. When this ratio was calculated for the patients in the present series, complete separation of mitral stenosis from mitral insufficiency was not

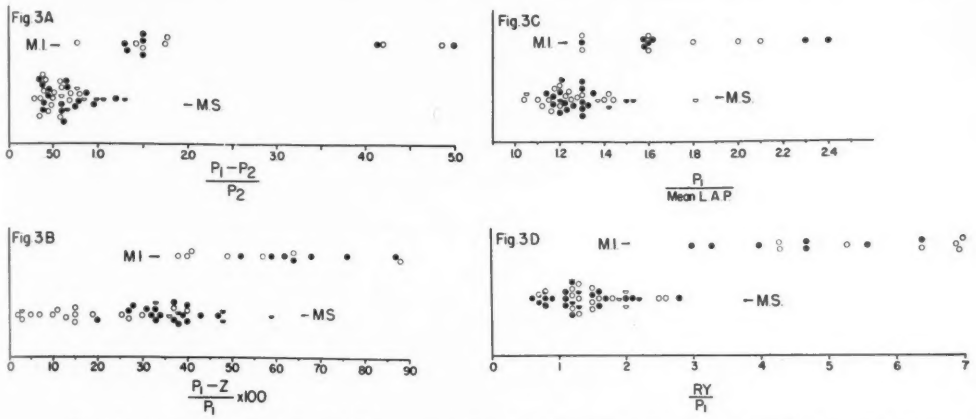

FIG. 3. Analysis of the left atrial pressure pulses by the previously reported methods. *MS* designates all patients with mitral stenosis requiring a mitral commissurotomy and *MI* those with pure mitral insufficiency. Each open circle represents a patient with sinus rhythm and each solid circle a patient with atrial fibrillation. Half circles designate those patients with mitral stenosis and significant mitral insufficiency.

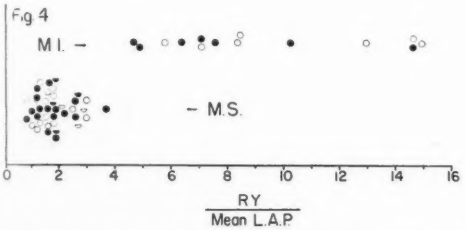

FIG. 4. Analysis of the left atrial pressure pulse in which the rate of the *y* descent (*Ry*) is related to the mean left atrial pressure (*MLAP*). The symbols correspond with those of figure 3.

apparent (fig. 3*A*). Allison and Linden[3] related the pressure at the peak of the *v* wave (P_1) to the pressure at the onset of ventricular contractions (*z* point). This may be expressed $\frac{(P_1 - z) \times 100}{P_1}$. When this formula was applied, there was distinct overlap, particularly among patients with sinus rhythm (figure 3*B*). Fox and associates[4] compared the height of the *v* wave (P_1) to the mean left atrial pressure. This ratio in the present series is plotted in figure 3*C*. There is no clear separation of the groups regardless of the rhythm. Owen and Wood[1] noted in *pulmonary capillary tracings* that the rate of the *y* descent was more rapid in mitral insufficiency than in mitral stenosis. This rate of descent (*Ry*) is expressed by the ratio $\frac{P_1 - P_2}{T_2 - T_1}$. (fig. 1). These investigators divided this rate of descent by the height of the *v* wave (Ry/P_1). When this formula was applied to the left atrial pressures of the present series of patients, better separation was obtained than with the other methods (fig. 3*D*).

It was noted that P_1 varied strikingly and the ratio Ry/P_1 changed significantly according to the phase of respiration and the length of the preceding diastole. Accordingly, the rate of the *y* descent (*Ry*) was related to a more stable denominator, the mean left atrial pressure (*MLAP*) (fig. 4). This ratio provided a better separation of patients with pure mitral insufficiency from those with mitral stenosis requiring a commissurotomy. In the patients in whom a mitral commissurotomy was indicated, the ratio $Ry/MLAP$ was always less than 4. When the ratio $Ry/MLAP$ exceeded 4, the predominant lesion was always mitral insufficiency.

It was observed that in the presence of atrial fibrillation, marked beat-to-beat variations in the ratio $Ry/MLAP$ occurred in a given patient. Analysis of the left atrial pulse revealed that in the presence of mitral stenosis the rate of the *y* descent was most rapid at its onset and diminished as diastole progressed. Therefore, in a patient with mitral stenosis, tachycardia

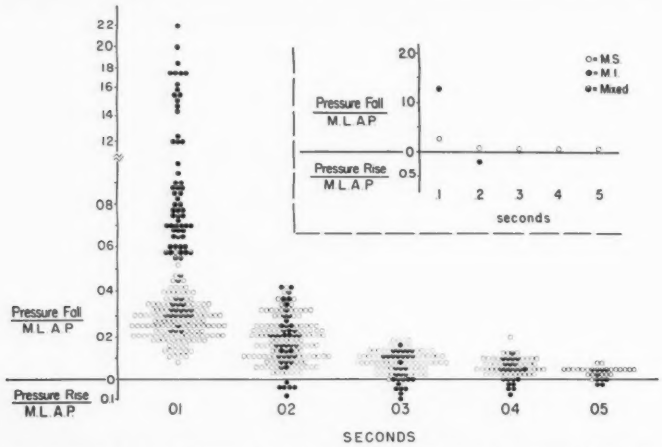

FIG. 5. The magnitude of the y descent divided by mean left atrial pressure ($MLAP$) at 0.1-second intervals. Four beats from each of the 53 patients are plotted, each symbol designates a single segment of a single beat. Open circles here represent patients with pure mitral stenosis and solid circles those with pure mitral insufficiency. Half circles represent those patients with predominant mitral stenosis and significant mitral insufficiency.

The insert illustrates the method of plotting applied to the individual beats in figures 2*A* and *B*. The y descent in figure 2*A* exceeds 0.5 second, and thus 5 points could be plotted. In figure 2*B* 26 mm. Hg represent the pressure fall in the first 0.1 second, while in the second 0.1 second a rise in pressure (diastasis) of 4 mm. Hg was noted.

abbreviates the duration of the y descent and thereby elevates Ry. Thus, the ratio $Ry/MLAP$ is a function of heart rate. Since the heart rate differs from patient to patient, and from beat to beat in a single patient with atrial fibrillation, the y descent was measured at standard time intervals.

It has been noted previously[12] that diastasis is absent in the left atrial pressure of patients with mitral stenosis, i.e., the y descent is uninterrupted until the onset of the next atrial or ventricular contraction. It was also felt desirable to incorporate this observation into the analysis of the left atrial pressure pulse.

Accordingly, the y descent divided by the $MLAP$ was calculated for each 0.10-second interval from its onset (P_1) to the beginning of the subsequent atrial contraction in patients with sinus rhythm or to the onset of the next ventricular contraction in patients with atrial fibrillation. This analysis is presented in figure 5. Four beats from each of the 53 patients were calculated. In figure 5 each symbol represents the value calculated from an individual beat. In beats in which the duration of diastole was abbreviated the ratio could only be calculated for the first 1 or 2 0.10-second periods. Hence fewer symbols are plotted as diastole progresses.

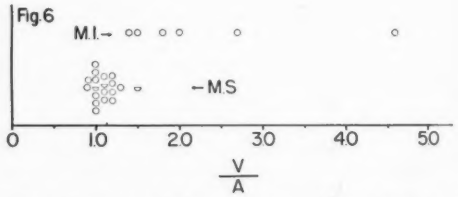

FIG. 6. Ratio of the pressure at the peak of the v wave to that at the peak of the a wave in patients with normal sinus rhythm. Half circles represent those patients with mitral stenosis and significant mitral insufficiency.

In the first 0.10 second there is a clear separation of virtually all beats from the patients with mitral insufficiency and those with mitral stenosis. Of the 14 patients with mitral insufficiency 7 had diastolic phases of sufficient duration to permit the calculation of the ratio for more than the first 0.10 second. Six of these 7 patients exhibited diastasis. This rise in the left atrial pressure is plotted as a "negative descent" and therefore appears below zero. Diastasis was absent in all 39 patients with mitral stenosis.

In the patients with sinus rhythm the pressure at the peak of the v wave (P_1) was related to the pressure at the peak of the a wave (a) and this relationship expressed as the ratio P_1/a. This analysis also offered a satisfactory differentiation between mitral stenosis and pure mitral insufficiency (fig. 6).

The method of analysis of Allison and Linden[3] (fig. 3*B*) revealed that in patients with atrial fibrillation higher values of $\frac{P_1-z}{P_1}$ were noted. However, the rhythm had no discernible effect in the other methods of analysis.

Discussion

It is realized that the methods described for analysis of the left atrial pressure curve are to a large degree empiric. The size and distensibility of the pulmonary venous bed and left atrium and ventricle profoundly affect the left atrial pressure pulse. It is apparent that a given volume of blood regurgitated into the left atrium may result in a large or small variation in atrial pressure depending upon the volume and distensibility of this chamber and the pulmonary venous bed. The mean left atrial pressure as utilized in the formulae described takes some consideration of these important variables.

In the normal subject or the patient with mitral stenosis, the v wave results only from filling of the atrium during the period in which the mitral valve is closed. In the presence of mitral insufficiency, however, blood from the left ventricle also enters the atrium at this time and further increases the pressure at the peak of the v wave. When the mitral valve opens, left atrial pressure falls as blood flows from the atrium into the ventricle. In the absence of mitral stenosis rapid filling of the ventricle occurs during early diastole. In middiastole a rise in ventricular and hence in atrial pressure takes place as blood enters the already well filled ventricle. This rise in pressure has been termed diastasis.[11] However, in the presence of mitral stenosis and a pressure gradient across the mitral valve, rapid ventricular filling cannot occur, the y descent is slow and prolonged, and diastasis is usually absent.[12] It should be noted, however, that diastasis might be expected to occur in those patients with mitral stenosis in whom the left atrioventricular pressure gradient falls to zero during long diastolic periods. In mitral insufficiency there is no obstruction to the flow of a volume of blood greater than normal and the fall in pressure is precipitous. Thus, in analyzing the formula presented ($Ry/MLAP$) it is apparent that in mitral insufficiency the pressure at the peak of the v wave is higher and also falls more rapidly than in mitral stenosis. Both of these factors tend to increase the value of Ry and hence elevate the ratio $Ry/MLAP$, and the rate of y descent during the first 0.1 second.

In the clinical use of left atrial pressure measurements it must be borne in mind that elevated left atrial pressures may occur with a normal mitral valve in the presence of the elevated left ventricular end-diastolic pressure that accompanies left ventricular failure. In the absence of tachycardia such left atrial pressure pulses generally exhibit diastasis, and this criterion may be employed to rule out the presence of mitral stenosis. The absence of diastasis is a specific abnormal feature of the left atrial pulse contour in mitral stenosis. This observation is not in accord with the view that the left atrial pulse of the patient with mitral stenosis and sinus rhythm closely resembles the normal in contour but is merely elevated in height.[13]

Extension of the technic of transbronchial puncture of the left atrium to include catheterization of the left ventricle permits measurement of pressure gradients across the mitral and aortic valves. When, however, clinical findings indicate a mitral lesion, left atrial puncture alone will aid materially in evaluation and selection of patients. When the left ventricle is not catheterized, the analysis of the atrial pressure pulse becomes even more important in the decision as to appropriate therapy. The transbronchial measurement of left atrial pressure can usually be carried out in less than 10 minutes. Its simplicity permits serial studies at frequent intervals. No untoward effects have been observed in more than 425 transbronchial punctures of the left atrium.

Combined lesions of the mitral valve present a "stenosis-insufficiency continuum" with all gradations in the severity of each. Accordingly, there is a group of patients in which determina-

tion of the predominant lesion has proved difficult. In the present series no method of analysis clearly separated those patients with pure mitral stenosis from those patients with accompanying mitral insufficiency of mild or moderate degree. However, in all these patients a commissurotomy was found indicated. On the basis of the findings presented, it is believed that the calculation of the ratio $Ry/MLAP$ (fig. 4), as well as the fractional analysis of the y descent and of diastasis (fig. 5), is of distinct value in distinguishing those patients with predominant mitral stenosis from those with pure mitral insufficiency. When sinus rhythm is present the ratio P_1/a is also of diagnostic value.

Summary

Left atrial pressures were determined by transbronchial puncture in 53 patients with mitral valve disease of proved type. Thirty-nine patients had mitral stenosis and required a commissurotomy; of these, 7 had significant associated regurgitation. Fourteen patients had pure mitral insufficiency.

The left atrial pressure pulses were analyzed by several previously described methods. Of these, the ratio Ry/v (Owen and Wood) proved most useful in distinguishing mitral insufficiency from predominant mitral stenosis.

The ratio $Ry/MLAP$ as well as the fractional analysis of the y descent and of diastasis afforded the best separation of the 2 groups. However, in the presence of predominant mitral stenosis, the severity of accompanying mitral regurgitation could not be determined with any method of analysis.

None of the left atrial pressure curves of the patients with mitral stenosis exhibited diastasis, and the significance of this observation is emphasized.

Acknowledgment

The technical assistance of Miss Estelle K. Resnick is gratefully acknowledged.

Summario in Interlingua

Le pressiones sinistro-atrial esseva determinate per punction transbronchial in 53 patientes con morbo de valvula mitral de typos demonstrate. Trenta-nove patientes habeva stenosis mitral e requireva commissurotomia. Septe de istes habeva grados significative de regurgitation associate. Dece-quatro patientes habeva pur insufficientia mitral.

Le pulsos de pression sinistro-atrial esseva analysate secundo methodos previemente describite. Le proportion Ry/v (de Owen e Wood) se monstrava utilissime in le differentiation de insufficientia mitral ab predominante stenosis mitral.

Le proportion de Ry a MLAP e le analyse fractional del descendita de y e del diastase cardiac representava le melior medios pro separar le duo gruppos. Tamen, in le presentia de predominante stenosis mitral, le grado de severitate del accompaniante regurgitation mitral non poteva esser determinate per ulle methodo analytic.

Nulle del curvas de pression sinistro-atrial ab patientes con stenosis mitral exhibiva ulle diastase. Le importantia de iste observation es signalate.

References

[1] Owen, S. G., and Wood, P.: A new method of determining the degree or absence of mitral obstruction. An analysis of the diastolic part of indirect left atrial pressure tracings. Brit. Heart J. **17:** 41, 1955.

[2] Facquet, J., Alhomme, P., Lemoine, J. M., Colvez, and Lagadoux: La pression auriculaire gauche, recueillie, par voie transbronchique, dan les cardiopathies mitrales. Arch. mal. coeur **47:** 136, 1954.

[3] Allison, P. R., and Linden, R. J.: Bronchoscopic approach for measuring pressures in the left auricle, pulmonary artery and aorta. Lancet **268:** 9, 1955.

[4] Fox, I. J., Wakai, C. S., Connolly, D. C., and Wood, E. H.: Left atrial and ventricular pressure pulses in mitral valvular disease. Proc. Staff Meet., Mayo Clinic **31:** 126, 1956.

[5] Wiggers, C. J., and Feil, H.: Cardiodynamics of mitral insufficiency. Heart **9:** 149, 1922.

[6] Haller, J. A., and Morrow, A. G.: Experimental mitral insufficiency. Surgery **38:** 518, 1955.

[7] Allison, P. R., and Linden, R. J.: The bronchoscopic measurement of left auricular pressure. Circulation **7:** 669, 1953.

[8] Facquet, C., Lemoine, J. M., Alhomme, P., and

LEFEBRIE, J.: La mésure de la pression auriculaire gauche par voie transbronchique. Arch. mal. coeur **45:** 741, 1952.

[9] MORROW, A. G., HALLER, J. A., AND RESNICK, E. K.: Left heart catheterization by means of transbronchial puncture of the left atrium. In preparation.

[10] OPDYKE, D. F., DUOMARCO, J., DILLON, W. H., SCHREIBER, H., LITTLE, R. C., AND SEELY, R. D.: Study of simultaneous right and left atrial pressure pulses under normal and experimentally altered conditions. Am. J. Physiol. **154:** 258, 1948.

[11] WIGGERS, C. J.: Studies on the consecutive phases of the cardiac cycle. I. Am. J. Physiol. **58:** 439, 1922.

[12] BRAUNWALD, E., MOSCOVITZ, H. L., AMRAM, S. S., LASSER, R. P., SAPIN, S. O., HIMMELSTEIN, A., RAVITCH, M. M., AND GORDON, A. J.: The hemodynamics of the left side of the heart as studied by simultaneous left atrial, left ventricular, and aortic pressures; particular reference to mitral stenosis. Circulation **12:** 69, 1955.

[13] WYNN, A., MATTHEWS, M. B., MCMILLAN, I. K. R., AND DALEY, R.: The left auricular pressure pulse in normals and in mitral valve disease. Lancet **2:** 216, 1952.

WILLIAM STOKES (1804–1878)

William Stokes was born in Dublin in 1804, the son of the Regius Professor of Medicine in the University of Dublin. The impact of Auenbrugger's Treatise on percussion, and the development of auscultation by Laennec aroused great interest at the time William Stokes attended medical school at Edinburgh.

In 1825 shortly before he graduated, he published the first systematic work in the English language on the use of the stethoscope. In other treatises, including that on Diseases of the Chest published in 1837, he described new diagnostic physical signs of pleural effusion and pneumonia and emphasized particularly the importance of correlating symptoms and physical signs in clinical diagnosis. He received international acclaim, including election to the National Institute of Philadelphia. On the death of his father, in 1845, Stokes was confirmed in the place he had held as locum tenens for twenty-seven years as Regius Professor of Medicine in the University of Dublin, a post which he occupied until his death.

His classic volume "The Diseases of the Heart and the Aorta" appeared in 1854 with its description of "Cheyne-Stokes Respiration" in connection with fatty degeneration of the heart. He refers to Cheyne's earlier description but emphasizes its diagnostic importance. Stokes in this volume also referred to his published articles on the slow pulse and its association with pseudo-apoplectic attacks with liability to sudden death now designated as "Stokes-Adams Syndrome" or disease. In this volume he advocates graduated muscular exercise for the rehabilitation of cardiac patients. Admirable descriptions of pericarditis and valvular heart disease are also presented. This work was translated into German, Italian, and French.

Practically all possible honors and degrees were accorded Stokes. Throughout his medical career he maintained close friendship with another illustrious member of the Dublin medical profession, Robert Graves. It was in large measure due to their combined efforts that the system of clinical instruction of the Dublin School of Medicine acquired world-wide fame. The statue of William Stokes, unveiled in 1876, two years before his death, now stands in the hall of the Royal College of Physicians in Dublin.—ED.

Pulseless Disease due to Branchial Arteritis

By Bohdan J. Koszewski, M.S., M.D., and Theodore F. Hubbard, M.S., M.D.

REPEATED reports from Japan and from north European countries have brought attention to a new clinical syndrome called "pulseless, or Takayasu disease." The condition is found in young women and is characterized by thrombosis of the vessels deriving from the arch of the aorta associated with cerebral, ocular, and upper extremity symptoms. Its etiology is obscure. We are presenting a case of this disease observed in a young Negro woman and studies carried out to clarify the pathogenesis of the disorder and its differentiation from the other known arterial diseases.

Case Report

The patient was first seen on our service in October 1954. She complained of generalized weakness and experienced several episodes of dizziness and palpitation. The attacks were related to exertion and were relieved in a few minutes by lying down. On 2 occasions the patient lost consciousness for a short period of time, but had no convulsions. In March 1953 she was hospitalized elsewhere, where a diagnosis of congenital heart disease was entertained. Thoracotomy revealed partial occlusion of the great vessels of the aortic arch in their proximal portions, and more completely distally. As surgical correction was impossible, nothing further was done. The past history was negative for colds or upper respiratory infections. There was no personal or family history of syphilis.

Physical examination revealed a well developed 13-year-old Negro girl. There were no trophic changes in nose or mouth. The pupillary reflexes and ocular fundi were normal. There was marked tenderness in the left supraclavicular area. The chest was clear, and there were no palpable pulsations or bruit over the intercostal arteries. The heart was not enlarged. There was a grade I soft systolic murmur in the aortic and right cervical areas. A loud, high pitched, systolic murmur was heard in the left supraclavicular area. The murmur was not transmitted to the carotid arteries and did not change in character with pressure of the stethoscope bell. Venous pressure and circulation times with ether and dehydrocholic acid were normal. Radial, brachial, and temporal arteries were not palpable. Carotid pulsation was absent on the left and was slight on the right. Compression of the carotid sinuses caused dizziness but no loss of consciousness or pulse changes. Femoral, popliteal, and pedal pulses were strong and symmetrical. Except for the left hand being 2 degrees cooler than the right, there were no skin temperature changes between the 2 sides. On oscillometry, oscillations were absent in the arms, but in the thighs and calves they were strong and symmetrical. The left hand showed pallor on elevation. Blood pressure was not obtainable in the arms. It was 150/90 mm. Hg in the right leg and 160/95 mm. Hg in the left. The abdominal aorta pulsated freely. The liver and spleen were not enlarged. There was no clubbing of the fingers. Neurologic examination revealed hyperactive tendon reflexes, but no other abnormalities. The intelligence quotient was low with an index of 58 by the Stanford-Binet method, but the patient seemed to be well adjusted.

Pertinent laboratory data were as follows: Urine showed 15 to 25 leukocytes per high-power field, staphylococci, and coliform bacilli. Urea clearance was 106 per cent of normal. Blood counts revealed hemoglobin, 10 Gm. per cent; erythrocytes 3,560,000, leukocytes 5,000, and platelets, 267,000 per mm.^{3} The differential count was normal, the bleeding time was 1 minute, coagulation time 7 minutes and reticulocytes were 0.4 per cent. There was no sickling of erythrocytes. Coombs test, cold agglutinins, and LE-clot test were negative. Sedimentation rate was 60 mm./hr. (Westergren). Blood serologic tests, as well as treponema immobilization test, were negative. Antistreptolysin-O titer was 166 units. Repeated blood cultures were negative. Blood chemistry was as follows: serum protein, 7.65 Gm. per cent; albumin-globulin ratio, 4.2/3.45; nonprotein nitrogen, 22 mg. per cent; cholesterol, 165 mg. per cent; prothrombin, 58 per cent; bilirubin, 0.45 mg. per cent; serum iron, 195 μg. per cent; total iron-binding capacity 395 μg. per cent. Electrophoresis of plasma proteins showed a slight increase in gamma globulins. The basal metabolic rate was minus 10 per cent. Excretion of 17-ketosteroids in urine was normal. An electrocardiogram was normal. Electroencephalogram showed paroxysmal bursts of 4 to 5 per second, high voltage waves occurring from all leads. No alteration was present with sedatives or photic stimulation. X-rays of chest, spine, skull, kidneys, and gallbladder were essentially negative.

Clinical Course. The patient showed slight fever that persisted even after the urinary infection was cleared with oxytetracycline. Treatment with vasodilators brought no improvement, and the dizzy spells persisted without change. In order to assess

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FIG. 1. Angiogram showing right carotid, subclavian, and innominate arteries, as well as aorta.

the possibility of surgical correction of the obstruction, the right common carotid artery was explored. The vessel was markedly thickened and edematous. A small biopsy was taken from the arterial wall. On histologic examination there was marked fibrosis and a nonspecific acute inflammatory reaction in the periarterial tissue and neighboring muscles. The infiltrates consisted predominantly of polymorphonuclear cells with a few lymphocytes and monocytes (fig. 1). The small arteries and veins visible in the specimen were patent and presented a normal wall.

Arteriography showed dye passing retrograde through the common carotid into the innominate artery and apparently normal aorta. The filling of the subclavian artery was good on both sides up to the region where the axillary artery begins. At this point there was apparently an occlusion, and the further course of the artery could be outlined for only a short distance through the filling of the vasa vasorum. None of the dye went into the internal carotid artery. The thyrocervical trunk was well visualized and there was good filling of the vertebral artery on both sides. Marked collateral circulation was evident about the scapula (fig. 2).

During the procedure the patient had a generalized convulsion. Her immediate recovery was prolonged because she developed a transient paralysis of both legs. Weakness in the right leg persisted for 2 months. Postoperatively a depression of the S-T segments and negativity of T waves were also evident in the electrocardiogram. These changes regressed spontaneously during a period of 3 weeks.

Following the arteriography the patient was placed on anticoagulants for a period of 4 weeks. Because of the evidence of inflammatory periarteritis, it was decided to use long-term steroid therapy. After a 3-month course of 100 mg. of cortisone daily, the patient felt greatly improved. She had no fainting spells and her neurologic symptoms disappeared completely. Her body weight increased from 108 to 133 pounds. Auscultatory blood pressure was still not obtainable in the arms; the flush method showed it to be 55 mm. Hg. The values in the legs were 180/80 mm. Hg. Oscillometric excursions were strong in the legs, but still absent in the arms. Sedimentation rate was only 4 mm./hr., antistreptolysin-O titer was 50 units, C-reactive protein test was negative. Cortisone treatment had seemed to arrest the progressing vascular disease and another arterial biopsy was performed from the right elbow. The artery showed no pulsations, but the wall was not thickened and there were no periarterial adhesions. On incision the intima was smooth and a small amount of blood was oozing slowly out of the vessel. Microscopic examination revealed a normal arterial wall with no sign of infiltration or fibrosis.

The cortisone treatment was maintained through the following 2 years with decreasing doses. The patient continued to feel well and was completely free of symptoms. Her sedimentation rate remained low, and there was no evidence of fever or anemia. A complicating tubo-ovarian abscess was treated successfully with oxytetracycline in 1955. In 1956 the patient became pregnant and delivered spontaneously a full-term healthy girl.

DISCUSSION

The symptoms and clinical findings in this case are quite typical of "pulseless disease" of the "young female arteritis" type.[1] The primary pathologic lesion apparently consisted of an acute, almost phlegmonous, periarteritis. The process was strictly segmental as only the large elastic arteries of the aortic arch were involved, while the arteries distal to the diseased area were free from inflammation or thrombosis. In the 12 autopsies reported in the literature[2-13] the arterial disease was also limited to this region. The thoracic aorta was quite often involved, but only in its proximal parts. The restriction of the arteritis to the originally branchial branches is very characteristic and deserves more attention in future etiologic and pathogenetic studies (congenital branchial arteritis?).

Histologic examination in these cases re-

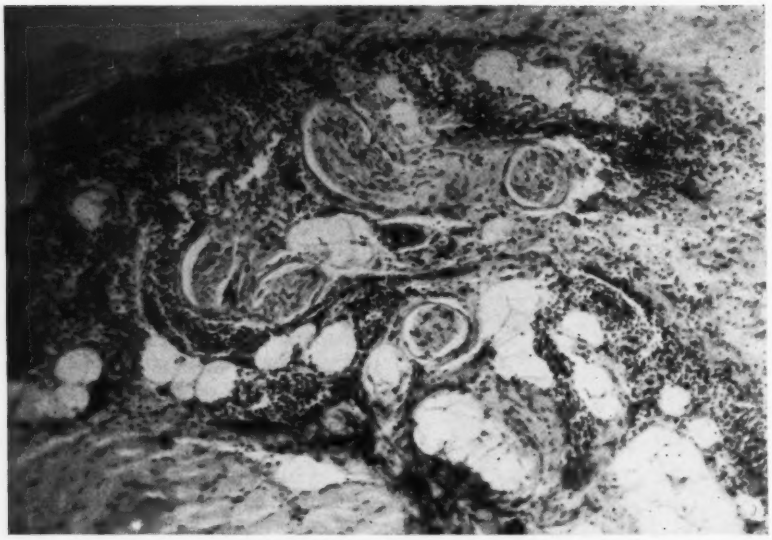

FIG. 2. Photomicrograph of biopsy from the right common carotid artery. Adventitia is thickened and contains many hypertrophic nerves. In the internal layers there is a dense infiltration of polymorphonuclear and mononuclear leukocytes.

vealed the fibrosis to be the result of a panarteritis. All 3 layers of the arteries were involved with most evidence pointing to a primary periarteritis. In Harbitz's case[4] the round-cell infiltration in the aortic adventitia was very pronounced. Similar inflammatory changes were present in the carotid and subclavian arteries. There were no giant cells in the media so characteristic of temporal arteritis[9, 14] and no fibrinoid degeneration in the intima as occurs in thromboangiitis obliterans.[15, 16] Beneke[5] also described primary periarteritis of the aorta with necrosis of the media and sclerosis of the intima. Oota[6] reported marked fibrosis of the adventitia of the aortic arch and its branches and atrophy of the media. The granulation tissue showed lymphocytic and plasmacellular infiltrations. In Frovig's case[7] the aorta and its branches revealed massive inflammatory foci in the media and adventitia. The medial coat showed a fibroblastic proliferation with numerous giant cells. However, the importance of these findings should not be overestimated as giant cells are a common finding in atrophy of muscular or elastic tissue.[17] Primary periarteritis with secondary thrombosis may also be suspected in the cases of Marinescu and Kreindler,[8] Gilmour,[9] and Maspetiol and Taptas,[11] although in these cases fibrosis and degenerative changes were predominant.

The pathologic changes are characteristic enough to regard the condition as an independent syndrome that can be differentiated from other inflammatory and degenerative arterial disorders. As shown in our case, the primary lesion apparently consists of an acute neutrophilic periarteritis that progresses to panarteritis and causes arterial thrombosis. Later stages are characterized by fibroblastic hypertrophy of adventitia and chronic inflammatory changes.

In view of these findings the report of the Committee on Nomenclature of the American Society for the Study of Arteriosclerosis[18] that the "aortic arch arteritis" is a proliferative disorder involving the intimal and medial coats needs a revision. The definition was possibly influenced by the case report of Barker and Edwards[19] of arteritis of the aortic arch in a 62-year-old woman. However, the patient was not a typical example of "pulseless disease," and the clinical and pathologic findings show a

far greater similarity to the central form of temporal arteritis, as reported previously by Sproul and Hawthorne,[20] and Gilmour.[9]

Prognostically, "pulseless disease" or "branchial arteritis," as we would call it, is a serious condition as most cases died before the fourth decade with death usually resulting from cerebral ischemia or coronary insufficiency.[7] The course of the disease is chronic and progressive but with variable remissions. Spontaneous regression appears possible as some cases showed only minimal inflammatory changes at the time of the autopsy.[8, 10, 11]

The treatment has in most cases had little effect on the course of the disease. Surgical measures such as thrombectomy, sympathetic denervation, and grafting of the carotid artery have not been successful.[21] Excision of the carotid sinus ameliorated the symptoms caused by the sensitive carotid sinus,[22] but did not arrest the progressive course of the arteritis.[13] Experience in this case with the use of steroids and anticoagulants is encouraging but does not allow any conclusions. Antibiotics and stercids had no apparent effect in other reported cases,[12, 13] but in no instance was the treatment of significant duration.

Summary

A case of pulseless disease or branchial arteritis is described and findings of arteriography and arterial biopsy are observed. The primary lesion seems to consist of an acute neutrophilic periarteritis progressing to panarteritis, causing arterial thrombosis. Later stages are characterized by fibroblastic hypertrophy of adventitia with lymphocytic and plasmacellular infiltrations.

The anatomic changes are characteristic enough to regard the condition as an independent syndrome that can usually be well differentiated from other inflammatory and degenerative arterial diseases.

The arteritis in this case seemed to respond to combined steroid and anticoagulant therapy.

Summario in Interlingua

Es describite un caso de morbo apulsatile o arteritis branchial. Constatationes de arteriographia e de biopsia arterial es presentate. Il pare que le lesion primari es un acute periarteritis neutrophilic progredente a panarteritis e causante thrombosis arterial. Stadios plus avantiate es characterisate per hypertrophia fibroblastic del adventitia e del media con infiltrationes lymphocytic e plasmacellular.

Le alterationes es satis characteristic pro establir le condition como un syndrome independente e usualmente ben differentiabile ab altere morbos arterial inflammatori e degenerative.

In le presente caso, le arteritis pareva responder a un therapia steroide e anticoagulante combinate.

References

[1] Ross, R. S., and McKusick, V. A.: Aortic arch syndromes. Diminished or absent pulses in arteries arising from arch of aorta. Arch. Int. Med. **9:** 701, 1953.

[2] Savory, W. S.: Case of a young woman in whom the main arteries of both upper extremities and of the left side of the neck were throughout completely obliterated. Med.-Chir. Trans. **39:** 205, 1856.

[3] Kussmaul, A.: Zwei Falle von spontaner allmahlicher Verschliessung grosser Halsarterienstamme. Deutsche Arch. klin. Med. **24:** 461, 1872.

[4] Harbitz, F.: Bilateral carotid arteritis. Arch. Path. **1:** 499, 1926.

[5] Beneke, R.: Ein eigentumlicher Fall schwieliger Aortitis. Virchows Arch. path. Anat. **254:** 723, 1925.

[6] Oota, K.: Ein seltener Fall von beidseitigem Carotis-Subclaviaverschluss. Ein Beitrag zur Pathologie der Anastomosis peripapillaris des Auges mit fehlendem Radialispuls. Trans. Soc. Path. Japan. **30:** 680, 1940.

[7] Frovig, A. G., and Laken, A. C.: The syndrome of obliteration of the arterial branches of the aortic arch due to arteritis. Acta psychiat. et neurol. scandinav. **26:** 313, 1951.

[8] Marinescu, G., and Kreindler, A.: Obliteration progressive et complete des deux carotides primitives. Acces epileptiques. Presse méd. **42:** 883, 1936.

[9] Gilmour, J. R.: Giant-cell chronic arteritis. J. Path. & Bact. **53:** 263, 1941.

[10] Joob, A.: Zwei eigenartige Falle von Arterienerkrankung. Schweiz. med. Wchnschr. **77:** 431, 1947.

[11] Maspetiol, R., and Taptas, J. N.: Thrombose de gros troncs de la crosse de l'aorte chez une jeune

femme. Ses raports avec les diverses arterites thrombosantes. Semaine Hôp. Paris **84:** 2705, 1948.

[12] LINDQUIST, T.: Arterit i de fran aortabagen utgaende artarerna. Nord. med. **37:** 321, 1948.

[13] ASK-UPMARK, E.: On the "pulseless disease" outside of Japan. Acta med. scandinav. **149:** 161, 1954.

[14] HORTON, B. T., MAGATH, T. B., AND BROWN, B. E.: Arteritis of the temporal vessels. A previously undescribed form. Arch. Int. Med. **53:** 400, 1934.

[15] BURGER, L.: The veins in thromboangiitis obliterans. J.A.M.A. **52:** 1319, 1909.

[16] JAGER, E.: Zur pathologischen Anatomie der Thromboangiitis Obliterans bei juveniler Extremitatengangran. Virchows Arch. path. Anat. **284:** 526, 1932.

[17] RAU, L.: Ueber Vorkommen, Bedeutung und Entstehung der Riesenzellen in normalen und pathologischen Zustanden. Erg. allg. Path. **26:** 228, 1932.

[18] WOLFFE, J. B., ET AL.: Report of Committee on Nomenclature of the American Society for the Study of Arteriosclerosis. Circulation **12:** 1065, 1955.

[19] BARKER, N. W., AND EDWARDS, J. E.: Primary arteritis of the aortic arch. Circulation **11:** 486, 1955.

[20] SPROUL, E. E., AND HAWTHORNE, J. J.: Chronic diffuse mesaortitis: Report of 2 cases. Am. J. Path. **13:** 311, 1937.

[21] SHIMIZU, K., AND SANO, K.: Pulseless disease. J. Neuropath. Clin. Neurol. **1:** 37, 1951.

[22] GIFFIN, H. M.: Reversed coarctation and vasomotor gradient: Report of a cardiovascular anomaly with symptoms of brain tumor. Proc. Staff Meet., Mayo Clin. **14:** 561, 1939.

Mackinnon, J., Vickers, C. F. H., and Wade, E. G.: The Effects of Adrenergic-blocking Agents on the Pulmonary Circulation in Man. Brit. Heart J. **18:** 442 (Oct.), 1956.

A dose of hydergine or priscol was injected down the catheter into the main stem of the pulmonary artery of 9 patients with mitral stenosis, 1 with mitral stenosis and regurgitation, 1 with mitral stenosis and aortic stenosis, 1 with pulmonary heart disease and 1 with pulmonary stenosis. Hydergine produced no constant effect on cardiac output, pulmonary arterial pressure, or pulmonary resistance. There was no evidence that it was a pulmonary vasodilator. Priscol had a variable effect except for an invariable increase in heart rate. Priscol also occasionally raised pulmonary artery pressure, perhaps by a direct effect upon arterial smooth muscle. It is therefore potentially dangerous in persons with pulmonary hypertension.

SOLOFF

Brucella abortus Endocarditis

A Case

By Raymond A. Hudson, M.D.

The diagnosis and successful treatment of a case of bacterial endocarditis due to *Brucella abortus* is described. Therapy consisted of the combination of aureomycin and streptomycin.

THE purpose of this report is to describe the successful treatment of a case of bacterial endocarditis due to *Brucella abortus*. As far as I have been able to discover at the date of writing, no successfully treated case of this disease has been reported previously, with the exception of a case of mixed bacterial endocarditis presented in 1954 by Quinn and Brown.[1] A second case of treated *Br. abortus* endocarditis, referred to by Keefer and Hewitt,[2] is sketchily described and the follow-up seems brief, being only 1 month.

Case History

J. T., a 33-year-old white man, a worker in a local radiator plant, was admitted to the E. J. Meyer Memorial Hospital on November 2, 1954, complaining of chills and fever for 3 days, malaise and lack of energy for 1 week, and some anorexia. He denied weight loss and claimed good general health although he knew he had rheumatic heart disease dating from an episode of chorea at age 7. In 1946, while living in Illinois, he had a transient right hemiplegia. There was no other history of serious illness. Recent sore throat or other respiratory illness was denied as was any history of joint pain. One tooth had been extracted 6 months before admission and he had had his teeth cleaned 2 months before admission. There was no history of ingestion of raw milk.

Physical examination on entry into the hospital revealed a young man who appeared both acutely and chronically ill. Rectal temperature was 104 F. The heart was slightly enlarged, with a regular rhythm and a rate of 116. A high-pitched systolic and early diastolic murmurs were noted at the base, down the left sternum to the apex. The mitral first sound was accentuated with an opening snap and mid and late diastolic rumbling murmurs at the apex. The blood pressure was 150/40, with a Corrigan pulse. The spleen was enlarged 2.5 cm. below the left costal margin, and was firm and nontender. There was no evidence of cardiac failure. The neurologic examination showed minimal evidence of an old left hemiplegia. The only embolic phenomena were 2 questionable splinter hemorrhages on the fingers of the left hand.

Laboratory findings on admission showed the following: urinalysis negative; hemoglobin 15.4 Gm. per cent; RBC 4.6 million; WBC 6200 with 55 filaments, 16 band forms, 29 lymphocytes, and 1 eosinophil. The erythrocyte sedimentation rate was 10 mm. with a hematocrit level of 47. The electrocardiograph was within normal limits. The lungs were clear on x-ray, with slight cardiac enlargement The antistreptolysin O titer was 100 units. Nose and throat cultures were negative for hemolytic streptococci.

The impression on admission was that the patient had rheumatic heart disease with aortic insufficiency and mitral stenosis, probably complicated by subacute bacterial endocarditis following dental surgery. While blood cultures were being obtained, salicylate therapy was administered, but it exerted no effect on the febrile state and was discontinued after 48 hours. The patient remained febrile but otherwise unchanged during the first week. On November 9, partial deafness was noted. On November 13, blood cultures taken November 4 and 10 were reported positive for *Staphylococcus albus hemolyticus*, coagulase negative, and more splinter hemorrhages were noted in the nailbeds and buccal mucosa. Treatment was therefore begun with aqueous penicillin 300,000 units every 3 hours intramuscularly. On November 17, the dosage was increased to 600,000 units every 3 hours, since there had been no temperature response. On November 20, more splinter hemorrhages and petechiae were noted and the fever persisted; penicillin was increased to 1,000,000 units every 3 hours. On November 23, since the isolated *Staph. albus* was insensitive to penicillin but sensitive to aureomycin, 500 mg. of the latter drug was given every 6 hours by mouth and the penicillin was omitted. That evening the patient developed a splenic infarction, and more buccal petechiae were seen. By November 27, the patient became afebrile and remained so. On this date, aureomycin had been increased to 3 Gm. a day. On December 2 *Br. abortus* was recovered from

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2 blood cultures taken on November 13. This organism was sensitive to aureomycin in a test tube dilution of 1.6 units per ml. It was sent to the New York State Health Department Laboratory in Albany, where identification was confirmed. *Br. abortus* agglutination on the patient's serum was 1:5120 on December 3. On December 10, combination streptomycin and dihydrostreptomycin, 0.5 Gm. b.i.d., was begun and continued during hospitalization and later at home.

All blood cultures, both aerobic and anaerobic, subsequent to November 13 were negative save for 1 on November 19, which showed diphtheroids. Such cultures were taken at least weekly. The agglutination against *Br. abortus* fell steadily to 1:80 at the time of discharge in February 1955. When last checked on August 28, 1956, no agglutinins were demonstrable. Repeated white cell counts ranged from 9,100 to 9,200, with a lymphocytosis of 49 to 53 per cent. The highest sedimentation rate recorded was 19 mm. per hour on January 21, 1955; it was 5 at the time of discharge. Repeated urinalyses showed little save a 1+ albumin on 2 occasions early in the course. The patient's serum of December 4, 1954, agglutinated the patient's brucella organism up to a dilution of 1:2560. (Patient's serum of December 3, 1954, agglutinated a stock antigen up to 5120.)

On February 7, 1955, the patient was discharged at his own demand. On that date he was afebrile and asymptomatic. The spleen was no longer felt and he had gained about 40 pounds in weight. The last splinter hemorrhage was noted on January 27, 1955, and for this reason as well as the type of basic disease, therapy was continued at home. No petechiae were noted after December 13, 1954. The early diastolic blowing murmur of aortic insufficiency changed in pitch during treatment, acquiring a shriller quality. Repeated electrocardiograms showed no change and the heart did not enlarge. No cardiac symptoms were found at discharge or later. After leaving the hospital, the patient intermittently showed a few splinter hemorrhages in the nailbeds of the hands as recently as January 10, 1956. When last seen, on August 28, 1956, he continued to remain asymptomatic, save for some slight residual deafness. There has been no evidence of recurrence, and the patient enjoys full activity. Total duration of treatment was 112 days of aureomycin 3 Gm. daily and 105 days of streptomycin 1 Gm. daily.

Discussion

Several features of this case are worthy of comment. First, the diagnosis of endocarditis due to *Brucella abortus* is difficult to make, as other authors have noted,[1] because brucellosis uncomplicated by endocarditis may present with similar features. It was considered that the diagnosis of bacterial endocarditis was well substantiated in view of the repeated showers of petechiae and splinter hemorrhages, the episode of splenic infarction, and the definite change in the quality of the aortic diastolic murmur. Direct bacterial valvular involvement seemed implicit in the changing murmur in the absence of some other factor such as failure, anemia, or rheumatic fever.

Second, it is interesting that the patient continued to show subungual splinter hemorrhages as recently as January 10, 1956. These seemed to occur after discharge from the hospital in relation to some manual task. No evidence of either bacterial recurrence or of blood dyscrasia was ever found to account for this. I have not been able to find a reference in the literature to the persistence of this phenomenon.

Third, the 2 cultures of hemolytic *Staphylococcus albus*, coagulase negative, on November 4 and November 10 have to be interpreted. The possibility of double infection as in the case of Quinn and Brown[1] cannot be ruled out entirely. However, the staphylococcus obtained was not found in cultures of the nose and throat or urine before or after antibiotic treatment and this organism had been a fairly common contaminant current in the bacteriology laboratory. Such an organism is not a pathogen under most circumstances.

As has been found in most reported cases of brucella endocarditis, the aortic valve is the seat of involvement here.[1-11] In common also with most of the previous cases, the underlying heart disease was rheumatic.

No source of brucella infection could be uncovered in spite of investigation by the Erie County Health Department. The patient denied ingestion of raw milk, but he had spent some time teaching in a rural area in New York State in the year prior to his illness and might possibly have encountered some infected dairy product without realizing it. The patient's deafness persisted in part, although it improved as he was treated. Deafness has been reported as a part of brucella infections and presumably is the result of direct damage to the acoustic nerve. Since it was present prior to treatment and improved as treatment continued, it was thought not to be related to the streptomycin.

Summary

A case of bacterial endocarditis due to *Brucella abortus* engrafted on a previous rheumatic valvular lesion has been described. It is of interest because treatment of the disease with aureomycin and streptomycin was successful.

Summario in Interlingua

Es describite un caso de endocarditis bacterial causate per *Brucella abortus*, graffate super un previe lesion valvular rheumatic. Le caso es interessante proque le tractamento del morbo con aureomycina e streptomycina esseva un successo.

REFERENCES

1. Quinn, R. W., and Brown, J. W.: Bacterial endocarditis. Arch. Int. Med. **94:** 679, 1954.
2. Keefer, C. S., and Hewitt, W. L.: The Therapeutic Value of Streptomycin: A Study of 3,000 Cases. Ann Arbor, Edwards, 1948, p. 57.
3. Quintin, T. J., and Stalker, M. R.: Endocarditis due to Brucella abortus. Canad. M. A. J. **55:** 50, 1946.
4. Hart, F. D., Lacey, B., and Morgan, A.: Brucella abortus endocarditis. Brit. M. J. **1:** 1048, 1951.
5. Wechsler, H. F., and Gustafson, E.: Brucella endocarditis of congenital bicuspid aortic valve. Ann. Int. Med. **16:** 1228, 1942.
6. Call, J. D., Baggenstoss, A., and Merritt, W. A.: Endocarditis due to brucella: 2 cases. Am. J. Clin. Path. **14:** 508, 1944.
7. Spink, W. W., and Nelson, A. A.: Brucella endocarditis. Ann. Int. Med. **13:** 721, 1939.
8. Beebe, P. T., and Meneely, J. K., Jr.: Brucella melitensis endocarditis. Am. Heart J. **38:** 788, 1949.
9. De la Chapelle, C. E.: Vegetative endocarditis due to Brucella melitensis. Am. Heart J. **4:** 732, 1929.
10. Smith, K. M., and Curtis, A. C.: Brucellosis with endocarditis. Am. J. M. Sc. **198:** 342, 1939.
11. Spink, W. W., Titrud, L. A., and Kabler, P.: Brucella endocarditis with clinical, bacteriologic and pathologic findings. Am. J. M. Sc. **203:** 797, 1942.

Whisnant, J. P., Millikan, C. H., Wakim, K. G., and Sayre, G. P.: Collateral Circulation to the Brain of the Dog following Bilateral Ligation of the Carotid and Vertebral Arteries. Am. J. Physiol. **186:** 275 (Aug.), 1956.

Most dogs survived ligation of all the major arterial vessels that supply the brain if these were tied in the neck. Ligation of 3 arteries had little clinical effect. After ligation, anastomotic branches were demonstrated by injections of liquid vinyl acetate. The main vessels providing the anastomoses after ligation were observed to be branches of the costocervical and omocervical arteries that join muscular branches of the vertebral arteries. This technic did not demonstrate anastomoses in the carotid system.

Oppenheimer

SYMPOSIUM ON CARDIOVASCULAR SOUND

GUEST EDITOR: VICTOR A. MCKUSICK, M.D.

II. Clinical Aspects

MODERATOR: DR. ROBERT P. GRANT

SOME NEWER OR POORLY RECOGNIZED AUSCULTATORY FINDINGS OF THE HEART

W. PROCTOR HARVEY, M.D., MICHAEL CORRADO, M.D. AND JOSEPH PERLOFF, M.D., *Washington, D. C.*

A SUMMARY of a miscellaneous group of clinical auscultatory findings is presented.

Ventricular Tachycardia. A succession of sounds (usually of low frequency) are commonly heard and are almost specific for ventricular tachycardia. These extra sounds are presumably due to wide splitting of the first and second sounds and gallop rhythm (fig. 1). When these sounds are combined with previously emphasized features, such as the changing intensity of the first heart sound, the very slightly irregular ventricular rate, and the lack of response to carotid sinus pressure, ventricular tachycardia can be even more strongly suspected at the bedside.

Ventricular "Knock" Sound. In mitral insufficiency a sound in early diastole is produced by the impact of an enlarged heart against the anterior chest wall in early diastole. Simultaneously the palpating hand feels a prominent impulse. This sound may be louder than even the first or second heart sound and is often misinterpreted as an opening snap or gallop. The mechanism of production is felt to be analogous to the pericardial "knock" sound with constrictive pericarditis. Whereas the constricting pericardial shell is responsible in pericarditis, the chest wall is the restricting structure with the ventricular knock (fig. 2).

Right-Sided Diastolic Murmurs of Severe Aortic Insufficiency. Diastolic murmurs best heard along the right sternal border rather than the left immediately suggest unusual disease in the region of the aortic valve or in the first portion of the ascending aorta (fig. 3). One of the following conditions is likely: aortic dissection or aneurysm, aortic cystic medionecrosis such as seen with the Marfan syndrome, aneurysm of a sinus of Valsalva, syphilitic aortic regurgitation.

Systolic "Whoop." This phenomenon, so named because of its similarity to the "whoop" of whooping cough, has been observed in 3 patients, all without heart disease. Each had a systolic click, which suddenly might be replaced by the "whoop" sound in systole. In the case presented (fig. 4) the sound appeared clinically to have no relation to position or phase of respiration. The condition is benign.

Splitting of Second Heart Sound with Right Ventricular Failure. As emphasized by Leatham, valuable information can be obtained by careful auscultation with particular reference to splitting of sounds. (1) A normal increase in degree of splitting of the second heart sound occurs with inspiration. (2) In congenital right bundle-branch block without right ventricular failure, wide splitting of the second sound occurs because of delayed pulmonic valve closure (fig. 5). In this case a further increase in the degree of splitting occurred with inspiration, as in normal subjects. (3) In right bundle-branch block with right ventricular failure, there is no increase in splitting with inspiration. This suggests that in right ventricular failure a point is reached when the normal augmentation of right ventricular filling associated with a prolonged right ven-

This is the afternoon session of a symposium held in Cincinnati on Friday, Oct. 26, 1956. Abstracts of the prepared talks were submitted by the speakers. The discussion was stenotyped. The proceedings of the morning session, devoted to the discussion of mechanisms, appeared in last month's issue of this journal.

tricular systole fails to take place. For example, in a patient with mitral incompetence without right ventricular failure, wide splitting of the second sound due to premature aortic valve closure increased in inspiration due to a normal delay in the pulmonic component (fig. 6*A*). In mitral incompetence with right ventricular failure increase in splitting did not occur with inspiration, presumably due to absence of delay in the pulmonic valve component (fig. 6*B*).

Murmur of Tricuspid Stenosis. An increase in intensity of the presystolic murmur may occur with inspiration (fig. 7).

In the same patient the simultaneous recordings of right ventricular and right atrial pressures by means of a double lumen catheter demonstrated that during expiration there was virtually no gradient across the tricuspid valve prior to atrial systole, but during inspiration as right atrial filling was augmented, the gradient appeared coinciding with the increase in the presystolic murmur.

Murmur of Tricuspid Incompetence Masquerading as Mitral Incompetence in Patients with "Tight" Mitral Stenosis. A significant number of patients are denied surgery for mitral stenosis because a systolic murmur of tricuspid incompetence is misdiagnosed as indicative of mitral incompetence. Such patients frequently have larger hearts than usually seen with mitral stenosis. The systolic murmur may be grade III or IV (or even louder) and may be heard over the mitral as well as the tricuspid area. If due to tricuspid incompetence, the intensity of the murmur is likely to increase on inspiration (fig. 8). The murmur of mitral incompetence, on the other hand, tends to decrease with inspiration.

Mitral Stenosis. The act of turning is important in "bringing out" the diastolic rumble of mitral stenosis. Textbooks emphasize the importance of the left lateral position in auscultation for the murmur of mitral stenosis. However, after finding the maximum apical impulse, it is of even greater importance to listen to the patient during the act of turning to the left lateral position. Sometimes the typical diastolic murmur is heard only for 6 to 10 beats as the patient turns, and then the murmur wanes quickly. If one waited until the patient had actually turned the murmur might be missed.

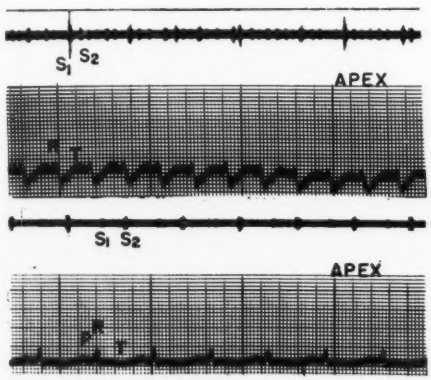

FIG. 1. Ventricular tachycardia, before and after reversion. *Upper tracing.* Succession of sounds with ventricular tachycardia. *Lower tracing.* Immediately after reversion. Extra sounds are absent with normal sinus rhythm. S_1, first sound; S_2, second sound.

Discussion

DR. HAROLD D. LEVINE (*Boston*): It is not necessarily *calcific* constrictive pericarditis in which the early diastolic sound occurs; you can get it whether or not there is calcification. It may be due to the so-called "cocktail shaker"

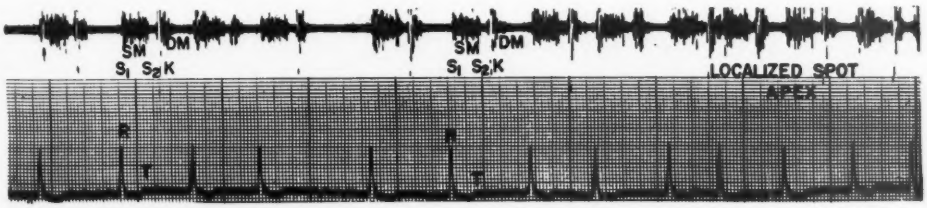

FIG. 2. Ventricular knock sound in cardiomegaly. Patient with mitral insufficiency, predominant, and stenosis. Ventricular "knock" (*K*) coincided with prominent palpable apical impulse. S_1, first sound; S_2, second sound; *SM*, systolic murmur; *DM*, diastolic murmur.

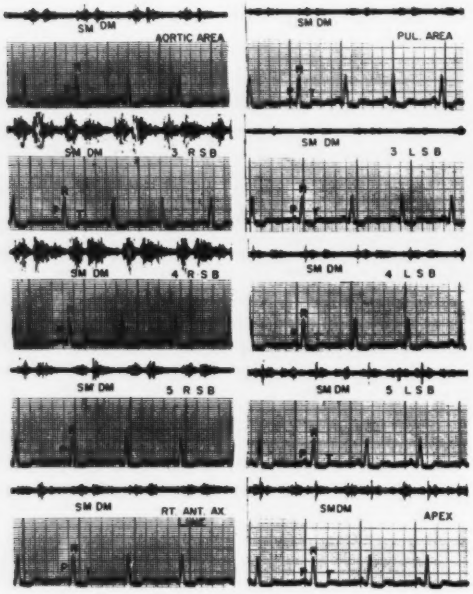

FIG. 3. Proved aneurysm of sinus of Valsalva in a 48-year-old woman with clinical features of severe aortic insufficiency. The murmurs are heard better along right sternal border (*RSB*) than along the left (*LSB*). *SM*, systolic murmur; *DM*, diastolic murmur.

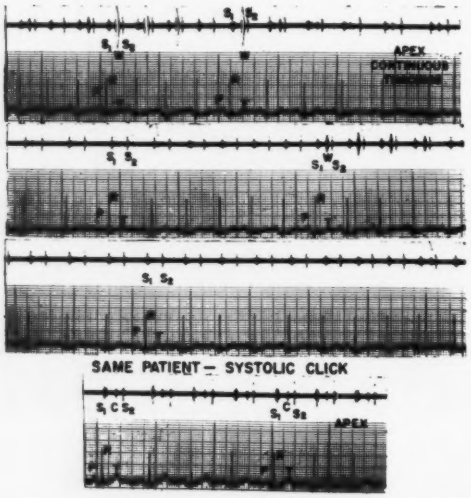

FIG. 4. A loud systolic "whoop" (*W*), in patient with a normal heart, waxes and wanes in intensity (upper 3 continuous tracings). Lower tracing: systolic click (*C*) heard intermittently between first and second sounds (S_1, S_2).

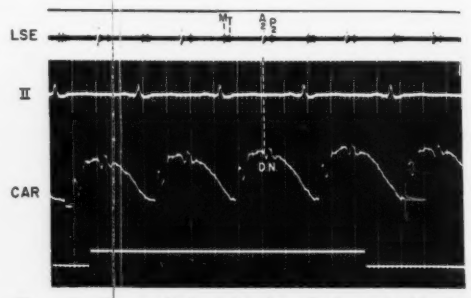

FIG. 5. Congenital right bundle-branch block. Exaggerated asynchrony of the 2 components of the first and second sounds resulting in abnormally wide splitting. With inspiration (upward deflection of the baseline) there is further delay in pulmonary valve closure and further widening of the second sound. (This and the phonocardiograms displayed in figures 6 and 7 were taken by Dr. Perloff during his rotation through Dr. Robert P. Grant's department at the National Heart Institute.)

motion of the heart and it may have a mechanism similar to that of the ordinary gallop.

Although the changing intensity of S_1 in paroxysmal ventricular tachycardia is quite diagnostic, there are cases of nodal tachycardia with bundle-branch block that show the same phenomenon.

I have studied a considerable number of cases of tricuspid regurgitation, mostly functional, in patients with congestive heart failure and found no change in intensity of the murmur with inspiration. There was already maximal flow across the valve and inspiration failed to produce further increase.

DR. ALDO A. LUISADA (*Chicago*): The correlation of the early diastolic sound in constrictive pericarditis (and in amyloidosis of the heart and cardiac fibrosis, as well) with reference recordings leaves no doubt that sudden checking of ventricular filling is the cause—whether or not we call it a protodiastolic gallop. With calcification of the pericardium the sound is higher pitched and louder.

DR. MARIANO M. ALIMURUNG (*Manila*): First I am wondering about Dr. Harvey's insistence that what he terms "ventricular knock" is not a gallop. Secondly, are there any new clues to the differentiation of the Graham Steell murmur from that of aortic regurgitation?

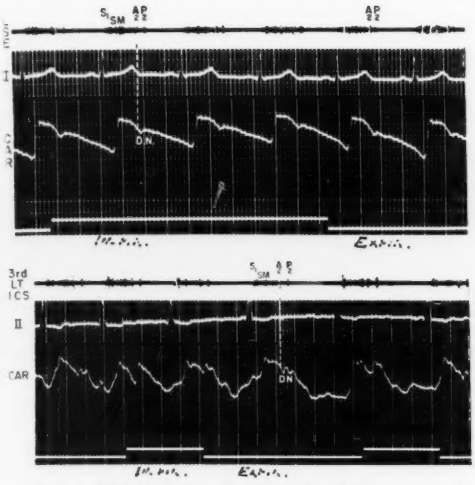

FIG. 6. Mitral Incompetence. No failure. *A* (*top*). The splitting of aortic (A_2) and pulmonic (P_2) components of second sound increase with inspiration (*inspir.*). *LSE*, left sternal edge; *CAR*, carotid pulses; *DN*, dicrotic notch; S_1, first sound; A_2, aortic component second sound; P_2, pulmonic component second sound. *B* (*bottom*). Mitral incompetence with right ventricular failure. Splitting of components of second sound (A_2, P_2) is fixed, with no change with respiration.

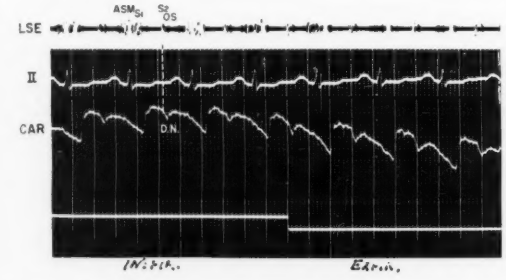

FIG. 7. Proved tricuspid stenosis. Note increase in presystolic murmur (*ASM*) with inspiration. S_1, first sound; S_2, second sound; *OS*, opening snap.

DR. HARVEY: We pay a great deal of attention to faint diastolic gallop sounds, heard with the bell held lightly, and often felt and seen as well as heard. Gallops are low-frequency sounds. But the sound we purposely call a knock is different. If you have your hand on the chest as you listen, you can feel the whole heart hit against the chest wall at the time of the extra sound. It seemed to us to be more analogous to the diastolic sound of constrictive

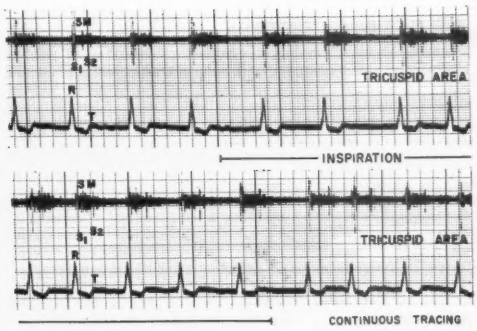

FIG. 8. Patient with proved tight mitral stenosis. A systolic murmur (*SM*) of tricuspid incompetence increases strikingly with inspiration.

pericarditis. It often is very loud, in fact often the loudest of the heart sounds. Perhaps we are stretching a point.

In deciding whether a diastolic murmur at the left sternal border is a Graham Steell murmur or represents aortic regurgitation, all the peripheral signs of the latter condition must, of course, be sought. One rule we hold to is that, if the diastolic murmur is at all audible to the *right* of the sternum, then it indicates aortic insufficiency.

DR. MCKUSICK (*Baltimore*): The view that hearing the diastolic murmur best along the right sternal border narrows the possibilities as to the cause of the aortic regurgitation is a special case of Balthazar Foster's rule. This "rule" is based on the premise that the direction of radiation of an aortic diastolic murmur is an indication of which cusp is primarily involved. This premise seems to have been proved unsound by the studies of Kerr and Palmer.[1] I have not been impressed with unusual radiation of the aortic diastolic murmur in patients with the Marfan syndrome.

SPLITTING OF HEART SOUNDS AND A CLASSIFICATION OF SYSTOLIC MURMURS[2-12]

AUBREY LEATHAM, M.D., *London, England*

Splitting of the first and second heart sounds, each into 2 major components, can be recognized by auscultation in most normal subjects. Assuming that mitral and tricuspid valve closures are mainly responsible for the first

sound,[2] and aortic and pulmonary valve closures for the second, splitting of these sounds may be attributed to slight asynchrony in onset and duration of left and right ventricular systole; this has been confirmed by pressure pulses taken simultaneously from the 2 ventricles and from the 2 great vessels.

Simultaneous high-frequency phonocardiograms (resembling the findings of auscultation) from the mitral and tricuspid areas show that the 2 major components of the first sound are normally separated by a narrow interval of 0.02 to 0.03 second. The first component is maximal at the mitral area, the second at the tricuspid area suggesting that mitral closure normally precedes tricuspid closure and this is confirmed by the relation of aortic ejection (indirect carotid tracing) to the first component rather than the second. Delay of right-sided events will also be found to account for splitting of the second sound in normal subjects (fig. 9).

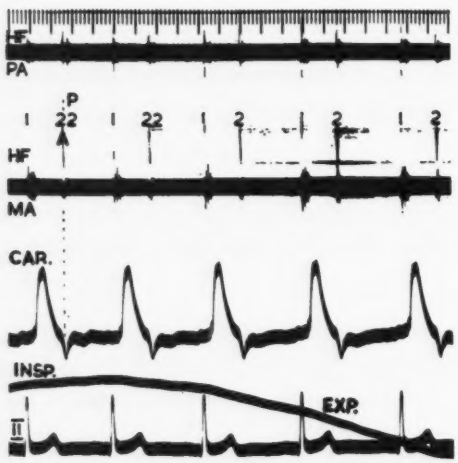

FIG. 9. Normal subject. Phonocardiograms from the pulmonary and mitral areas (*PA* and *MA*), an indirect carotid tracing (*CAR*), and electrocardiogram, all taken simultaneously. Splitting of the second sound is confined to the pulmonary area and to inspiration (*insp.*). The earlier component (A_2) is shown to be due to aortic closure by its synchrony with the dicrotic notch of the carotid tracing; it is transmitted to the mitral area. Later pulmonary closure (P_2) is confined to the pulmonary area. Time intervals in this and subsequent records are 0.2 and 0.04 second.

Increase in right-sided delay from complete right bundle-branch block is associated with abnormally wide splitting of the first sound best heard at the lower left sternal edge (tricuspid area). The electrocardiogram of "partial right bundle-branch block" (QRS less than 0.12 second) is not associated per se with abnormal splitting of either the first or second sounds and we have shown that there is no delay in onset of the right ventricular pressure pulse in these cases. Splitting of the major high-frequency components of the first sound is seldom obvious in complete left bundle-branch block,[13] partly because the normal slight delay in tricuspid closure makes it more difficult for mitral delay to cause obvious separation. Another explanation may be absence of delay in onset of left ventricular systole in left bundle branch,[14, 15] although the total duration of left ventricular systole is prolonged. Paradoxical closure of the tricuspid valve before the delayed and accentuated sound of mitral closure may be demonstrated in mitral stenosis by taking simultaneous phonocardiograms from the mitral and tricuspid areas.

The presence of an early systolic ejection sound may simulate wide splitting of the first sound but the extra sound, which is probably an exaggeration of normal ejection vibrations, is maximal at the base, and a simultaneous phonocardiogram from the tricuspid area shows that it is preceded by both mitral and tricuspid components of the first sound. The pulmonary ejection sound is maximal in the pulmonary area and decreases in intensity during inspiration. It is associated with dilatation of the pulmonary artery from increased flow in left-to-right shunts, from mild or moderate pulmonary valve stenosis, or from pulmonary hypertension when it occurs a little later owing to the prolonged isometric time of the right ventricle. An aortic ejection sound from dilatation of the aorta is often associated with coarctation of the aorta, pulmonary atresia, aneurysm, hypertension, arteriosclerosis, and aortic valve disease.

Splitting of the second heart sound in the pulmonary area during the inspiratory phase

of respiration is an obvious physical sign in most children and young adults, and was recognized by Potain (1866). Simultaneous phonocardiograms (fig. 9) from the pulmonary and mitral areas, together with a carotid tracing, show that the earlier component is due to aortic valve closure, and is the only one normally transmitted to the apex, and the later component is due to pulmonary valve closure and is normally isolated to the pulmonary area and immediately below it. In the expiratory phase of continued respiration the 2 valves close almost simultaneously. During inspiration the increased filling of the right ventricle from the extrathoracic venous reservoir selectively prolongs right ventricular systole, delaying closure of the pulmonary valve by as much as 0.08 second. Transmission of the pulmonary component to the apex is found when this area is over a dilated right ventricle as in atrial septal defect, or, when pulmonary closure is accentuated from pulmonary hypertension.

Abnormally wide splitting of the second sound, even in the expiratory phase of respiration, is caused by delay in pulmonary valve closure from complete right bundle-branch block, selective increase in right-sided flow as in atrial septal defect (or anomalous pulmonary venous return), and in pulmonary stenosis. In atrial septal defect the wide split (0.04 to 0.05 second) is almost fixed, scarcely varying with respiration, since little further filling of the right ventricle can be accomplished (fig. 10). There is no appreciable change in the width of the splitting directly attributable to pulmonary hypertension unless a right-to-left shunt abolishes the selective increase in right-sided flow. Pulmonary stenosis, whether valvular or infundibular, causes the greatest delay in pulmonary valve closure (up to 0.16 second or more) and the width of the splitting bears a close relation to the right ventricular systolic pressure. The splitting may be difficult to appreciate, since aortic closure is liable to be drowned in the pulmonary area where the systolic murmur is loudest, and the late pulmonary closure sound may be soft, but it can be heard and recorded in about 85 per cent of

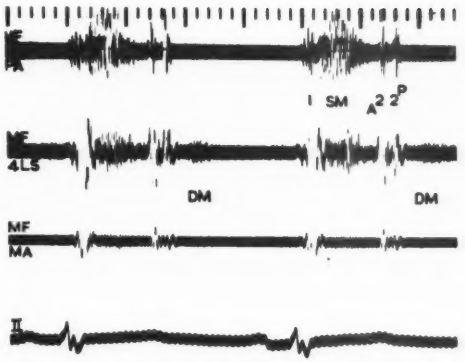

FIG. 10. Atrial septal defect with left-to-right shunt. Wide fixed splitting of the second sound due to delay in pulmonary component. Midsystolic ejection murmur (*SM*) due to increased pulmonary flow. (Courtesy, *Brit. Heart J.*)

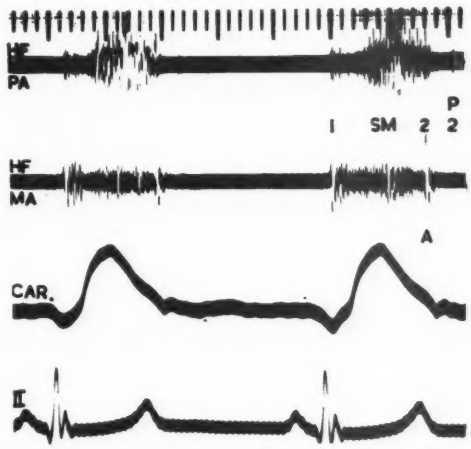

FIG. 11. Pulmonary stenosis (RV 65/5 mm. Hg). Midsystolic ejection murmur goes up to aortic closure but ceases before late soft pulmonary closure.

cases (fig. 11). When the pulmonary stenosis is associated with a ventricular septal defect and right-to-left shunt (Fallot's tetralogy) pulmonary flow is further reduced and the pulmonary valve closure sound is almost invariably absent. Abnormally wide splitting of the second sound is also found in mitral incompetence, and is caused by shortening of left ventricular systole due to diminished resistance to left ventricular outflow. This is probably a factor in causing a slight increase in

the width of splitting in ventricular septal defect (with left-to-right shunt) although the increased flow is affecting both ventricles.

Prolongation of left ventricular systole causes reversal of the normal order of valve closure, and thus paradoxical splitting of the second sound. This may be recognized by noticing that the split is maximal in expiration, decreasing on inspiration owing to the usual delay in pulmonary closure; the best example is complete left bundle-branch block. Paradoxical splitting of the second sound also occurs in severe aortic stenosis and in some cases of patent ductus arteriosus with left-to-right shunt.

Systolic Murmurs. Two varieties may be recognized: (1) Ejection—midsystolic—due to flow of blood through the pulmonary or aortic valve; (2) regurgitant—pansystolic—due to mitral or tricuspid incompetence, or, ventricular septal defect or patent ductus with left-to-right shunt.

Ejection systolic murmurs swell to a peak about midsystole and invariably finish before the second sound—or at least before the sound of closure of the valve where the murmur originates. This gap is to be expected, since flow must have almost ceased before valve closure. These murmurs originate at the aortic or pulmonary valve under the following condition, alone or in some combination: Stenosis of valve or infundibulum, valvular damage without stenosis, dilatation of vessel beyond, and increased flow or rate of ejection.

Aortic systolic murmurs (fig. 12) may be well transmitted to the apex; the presence of a silent interval between the end of the murmur and the second sound is a useful method of differentiation from a mitral systolic murmur. When the order of closure of the arterial valves is paradoxical as with severe aortic stenosis or left bundle-branch block the murmur may reach the earlier pulmonary closure but always stops before the later aortic closure. The greatest difficulty in recognizing the shape of the murmur is experienced when aortic closure is soft or absent as in rare cases of severe aortic stenosis.

In aortic incompetence a systolic murmur of similar shape (sometimes even accompanied by a systolic thrill) results from a stroke output which is increased both in rate and volume, across the deformed valve, while the dilated aorta beyond may be a third factor. In coarctation of the aorta the murmur due to ejection of blood through the stenosed vessel is of the same shape but may be shifted a little later.

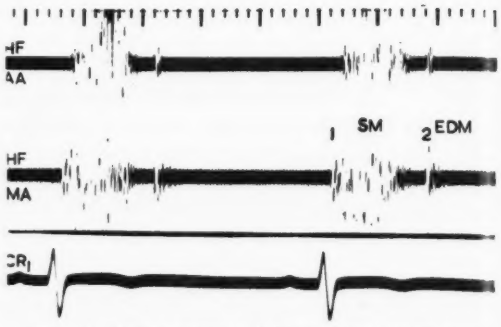

FIG. 12. Aortic stenosis. Midsystolic ejection murmur at aortic area (*AA*) finishing before aortic closure.[25]

In pulmonary stenosis (fig. 11), because of prolonged right ventricular systole and late closure of the pulmonary valve, the murmur may pass and drown the earlier aortic closure sound but always stops before the pulmonary closure sound when it can be recorded (*vide supra*).

The ejection murmur occurring with dilatation of the vessel beyond the valve in pulmonary hypertension is frequently initiated by an early systolic ejection sound.

Increased flow into the pulmonary artery is a frequent cause of pulmonary ejection systolic murmurs. One of the best examples is atrial septal defect (or anomalous pulmonary venous return); others are anemia, thyrotoxicosis, pregnancy, and increased stroke volume from slow rates as in complete heart block. Faint ejection vibrations can be recorded at the base in most subjects. When these become audible they probably represent the majority of innocent systolic murmurs. These murmurs are always short and soft on auscultation, finishing well before the second sound and frequently possessing a grunting or musical quality. They are most frequent in children, become louder with increased blood flow as with exertion or

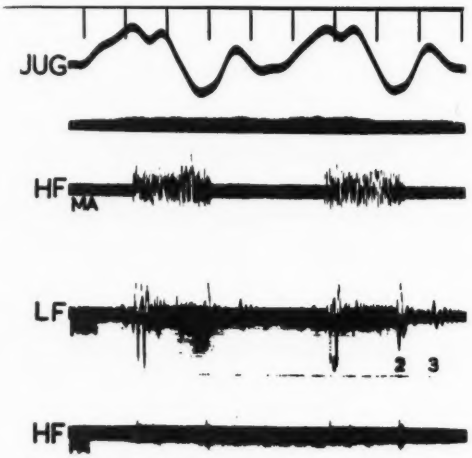

FIG. 13. Mitral incompetence. Pansystolic regurgitant murmur.

excitement, and tend to disappear as the child becomes older.

Regurgitant systolic murmurs are always pansystolic (when filters are used to make the graph resemble the findings of auscultation), since, in the situations in which this type of murmurs occurs, pressure in the donor chamber or vessel is higher than that in the recipient chamber throughout systole. Take, for example, the left ventricle and left atrium in mitral incompetence. There is persistence of a big pressure difference at the time of aortic closure and the continuation of the murmur at this point means that the second sound at the apex tends to be obscured. The accentuated but low-pitched third heart sound of mitral incompetence must not be mistaken for the second sound (fig. 13).

In some cases of mitral incompetence the murmur is maximal in late systole, yet is found in recordings to be pansystolic. The mechanism of the late systolic crescendo is not understood. Late systolic murmurs without vibrations in early systole appear to be innocent. They are seldom loud, tend to be initiated by a systolic click, and often vary with respiration.

Although characteristically the murmur of uncomplicated ventricular septal defect is pansystolic, it becomes minimal or absent with high pulmonary resistance and pressure and diminished left-to-right shunt, but there may be an ejection systolic murmur (and a pulmonary diastolic murmur) in the pulmonary area from dilatation of the pulmonary artery. The same mechanism accounts for the disappearance of the typical continuous murmur in patent ductus with high pulmonary resistance. In some of these cases there is a pansystolic murmur in the pulmonary area suggesting that the left-to-right shunt may be systolic only, and can be attributed to the difference in pressure and resistance between the 2 great vessels being confined to systole.

Discussion

DR. LEVINE: I was surprised by Dr. Leatham's statement that he had felt a systolic thrill in cases without actual aortic stenosis.

DR. LEATHAM: Yes. We observed 3 cases of syphilitic aortic incompetence in which there was a systolic thrill but no stenosis found at necropsy.

PHYSICIAN: Would you comment on the intensity of the pulmonary closure sound in pulmonary stenosis?

DR. LEATHAM: In mild pulmonary stenosis it is little if at all reduced in intensity. Possibly the dilatation of the pulmonary artery favors conduction of the sound to the surface of the chest in these cases. I find the loudness of the pulmonary component of the second sound little help in deciding severity of the stenosis; it varies a great deal with the anatomy of the chest wall, degree of dilatation of the pulmonary artery, anatomy of the stenotic valve, and so on. I find the delay in pulmonary valve closure a much more valuable index of severity.

DR. FRANKLIN D. JOHNSON (*Ann Arbor*): In connection with the splitting of heart sounds, it might be well to point out what a wonderful instrument the human ear is. I am talking now purely about things that we hear with the stethoscope. The question comes up, How close together can 2 sounds be and yet be appreciated as 2, not 1? One can investigate this with the shutter of a camera which makes 2 similar sounds, 1 of opening and 1 of closing, separated by an interval that can be set. Even at an interval of a fiftieth of a second (.02 second) 2 sounds can be distinguished; at shorter intervals, they tend to merge. But it is an individual

matter. I am sure some people can appreciate a split as close as .01 second.

DR. JOSEPH K. PERLOFF: The slide of congenital right bundle-branch block shown earlier (fig. 5) demonstrates splitting of the first heart sound. Of the 2 components the first is louder at the apex and the second at the sternal edge. So it is thought that the sources are mitral closure and tricuspid closure, respectively.

EFFECT OF RESPIRATION AND UPRIGHT POSITION ON THE INTERVAL BETWEEN THE TWO COMPONENTS OF THE SECOND HEART SOUND AND THAT BETWEEN THE SECOND SOUND AND THE MITRAL OPENING SNAP

BORYS SURAWICZ, M.D., *Burlington, Vt.*

When the pulmonary valve closes later than the aortic valve, the interval between the 2 components of the split second sound seldom exceeds 0.04 second in normal adult individuals. However, it may occasionally exceed this value in healthy teen-agers, as well as in conditions accompanied by an increased blood flow through the right ventricle and in the presence of right bundle-branch block.[16, 17] In these situations, the second component of the split second sound may be confused with the opening snap of the mitral valve.

The duration of the interval between the second sound and the opening snap usually measures 0.07 to 0.11 second. However, this interval can be as short as 0.03 or 0.04 second,[18, 19] especially in patients with a very reduced mitral valve area or rapid heart rate. An early opening snap may be confused with the second component of the second heart sound.

It was thought that these two situations could be distinguished more readily if the conditions of the examinations were altered. The following reasoning was applied: Conditions that increase the flow of blood into the right heart lead to a prolongation of the interval between the 2 components of a split second sound as they cause further delay in the closure of the pulmonary valve. The same conditions will cause increased filling and pressure in the left atrium* and thus an earlier opening of the mitral valve. On the other hand, conditions that decrease the flow of blood into the right heart lead to a shortening of the interval between the 2 components of the second sound caused by the late closure of the pulmonary valve. Since these conditions will also lead to a decreased filling of the left atrium, they will be expected to cause a later opening of the mitral valve and to increase the interval between the second sound and the opening snap.

Nine patients with established mitral stenosis and an audible opening snap and 15 persons with a split second sound due to late closure of the pulmonary valve in whom the interval between the 2 components of a split second sound exceeded 0.04 second, were studied. Phonocardiograms were recorded from the point where the opening snap or the second component of the second sound was heard best, using a Sanborn Twin-Beam Phonocardiograph with logarithmic setting of the amplifier. The

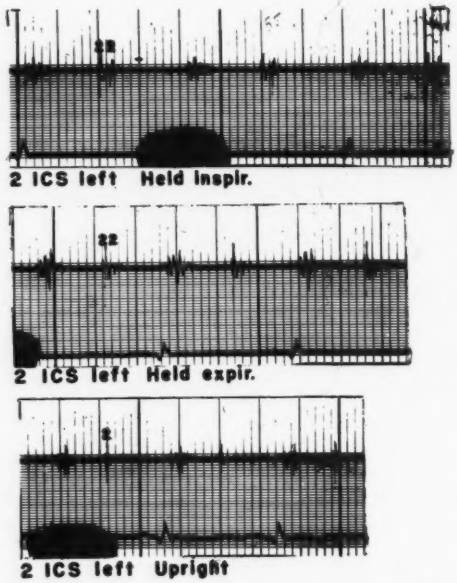

FIG. 14. Phonocardiogram and lead II of the electrocardiogram of a 15-year-old healthy, normally developed girl. In a recumbent position during held inspiration, the interval between the 2 components of the second sound measures 0.06 second. During held expiration the intensity of the second component of the second sound is decreased and the splitting of the second sound is less wide (0.05 second). In the upright position the second sound consists of 1 component only.

* *Ed.:* At least in normal subjects inspiration might be expected to have opposite effects on filling of the 2 sides of the heart.[20]

recordings were made during quiet normal respiration and during held inspiration, at first in the recumbent position, then immediately after standing up.

The following results were obtained: The effect of held inspiration and held expiration on the interval between the 2 components of the second sound conformed with the well-known results of previous observations, namely lengthening in inspiration and shortening in expiration.[11, 16] The opening snap showed a tendency to appear later after prolonged expiration and earlier after prolonged inspiration. However, these variations did not appear to be consistent and, moreover, the results were obscured by variations of the heart rate which took place during respiratory maneuvers. The effects of changing heart rate on the timing of the opening snap have been described by several investigators; they consist of earlier appearance of the snap after a short diastolic interval and a later appearance after a long

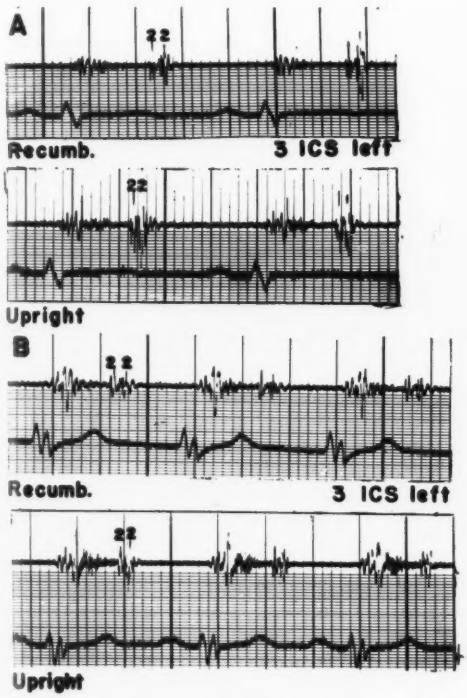

FIG. 15. *A*. Phonocardiogram and lead II of the electrocardiogram of a 34-year-old man with atrial septal defect. The calculated left-to-right shunt was 6.62 L. per minute and the right ventricular pressure was 49/8 mm. Hg. Note the wide splitting of the second sound (0.06 second) in the recumbent position and a decrease in splitting (0.03 second) in the upright position. The heart rate is almost identical in both tracings. *B*. Phonocardiogram and lead II of the electrocardiogram of a 24-year-old woman with atrial septal defect. The calculated left-to-right shunt was 8.96 L. per minute, and the right ventricular pressure 42/10 mm. Hg. The electrocardiogram shows an incomplete right bundle-branch block with QRS duration of 0.11 second. Note the wide splitting of the second sound (0.07 second) in the recumbent position and a decrease in splitting (0.04 second) in the upright position. The heart rate is nearly identical in both tracings.

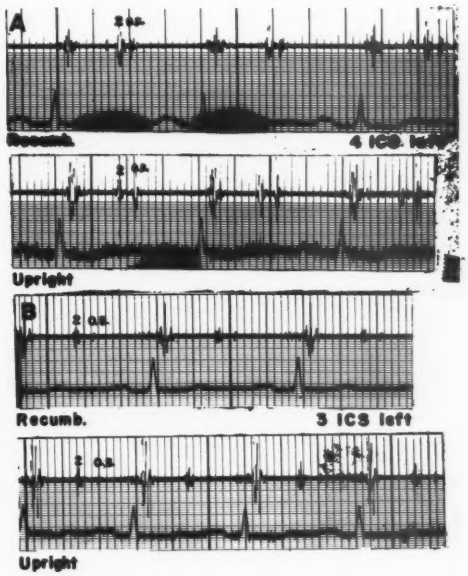

FIG. 16. *A*. Phonocardiogram and lead II of the electrocardiogram of a 42-year-old woman with rheumatic heart disease and mitral stenosis. The calculated mitral valve area (Gorlin's formula) was 0.6 cm.^{2}, and the pulmonary artery pressure 56/28 mm. Hg. Note that the duration of the interval between the second sound and the opening snap (*OS*) measures 0.06 second in the recumbent and 0.09 second in the upright position. The heart rate is nearly the same on both occasions. *B*. Phonocardiogram and lead II of the electrocardiogram of a 43-year-old woman with rheumatic heart disease and mitral stenosis. Calculated mitral valve area = 1.2 cm.^{2}; pulmonary artery pressure = 37/23 mm. Hg. Note that the duration of the interval between the second sound and the opening snap (*OS*) measures 0.09 second in the recumbent and 0.11 second in the upright position. The heart rate is more rapid in the upright position.

diastolic interval. No variations of the timing of the opening snap were noted during respiration by Mounsey[18]; however, presence of variations was reported by Schoelmerich and Gehl.[21]

In the upright position shortening of the interval between the 2 components of the second sound and lengthening of the interval between the second sound and the opening snap occurred in nearly all examined cases. The changes produced by standing were more marked than those produced by changing the respiratory position (fig. 14*A*). A lengthening of the interval between the second sound and the opening snap in the upright position was described earlier by Schoelmerich.[21, 22] In the present study, the greatest differences in the duration of the discussed intervals were seen when the phonocardiogram taken in the recumbent position during held inspiration was compared with the phonocardiogram taken in the upright position during held expiration. However, unequivocal differences were usually noted between the phonocardiogram taken during quiet respiration in the recumbent and upright position. These differences frequently took place without any change in heart rate (figs. 15 and 16*A*). Figure 16*B* shows a prolongation of the interval between the second sound and opening snap in the upright position at the time when the heart is more rapid. In this case one would expect an earlier appearance of the opening snap with a more rapid heart rate, but the effect of upright position apparently nullifies the expected effect of the increased heart rate.

Clinical Survey

Victor A. McKusick, M.D., *Baltimore, Md.*

Spectral phonocardiograms (SPCG) will be used to illustrate the following comments. In these displays of sound, time is on the abscissa and frequency on the ordinate; intensity is represented as degree of blackness in given portions of the display.[23] These records appear to have the following advantages, all resulting from the spreading out of frequency: 1. Fine splitting, i.e., separation of the components of complex transients, can be more easily identified—to an interval of .01 second or less under ideal circumstances.[16] 2. Timbre is represented—a feature which renders the method useful for the study of musical murmurs (see below). 3. A loud and a faint murmur can be displayed in the same record in something more nearly approaching their true intensity proportions.[24] 4. Artifacts are more easily identified.

The method has, however, not yet come of age, from the standpoint either of instrumentation or of clinical application. In my opinion an adequate instrument is not presently available commercially. Desirable for such an instrument are the following: (1) flexibility in the manipulation of the time axis without influencing the frequency scale—so that these sounds can be stretched out for closer analysis; (2) possibly photographic display for improved intensity grading; (3) improved analysis in the low frequency range—below 60 or 100 c.p.s.; and (4)—at least for a research instrument—facilities for putting multiple channels of information on the record, e.g., 2 spectral phonocardiograms, conventional oscillographic phonocardiogram, carotid pulse, etc., in addition to the electrocardiogram, which is the barest essential for any instrument.

Musical Murmurs.[25] The SPCG provides a physical definition for musicality in murmurs: instead of the rather diffuse frequency pattern of the usual noisy murmurs, harmonic pattern characterizes musical murmurs. Justification for dividing murmurs into noisy and musical types is provided by 2 rather distinctive features of musical murmurs as a genus: 1. A structural member which is thrown into vibration can be identified post mortem in most, perhaps all instances—retroverted aortic cusp, aberrant ventricular tendon, stenotic aortic valve diaphragm, rubbing pleuropericardial surfaces, etc. Although fluid factors and boundary structural factors are obviously of significance in the generation of both noisy and musical murmurs, fluid factors seem dominant in the case of noisy murmurs and the structural factor in musical murmurs. 2. Musical murmurs include some of the loudest varieties of cardiovascular sound; e.g., the musical murmur of retroverted aortic cusp or of calcific aortic stenosis may be audible at a distance from the body.

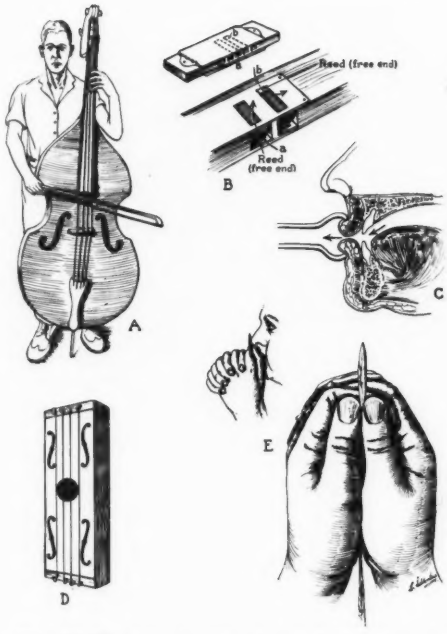

FIG. 17. The counterparts in musical instruments of the generators of musical murmurs in man. *A*. Bass viol (violin family in general); analogous to musical pleuropericardial murmurs. *B*. Harmonica; not strictly analogous to retroverted aortic cusp, since the reed faces into the wind not downstream. Reed *a* is activated on blowing and alternate reed *b* on sucking. *C*. Trumpeter's lip; analogous to calcific aortic stenosis. *D*. Aeolian harp; analogous to anomalous chordae tendineae. *E*. Reed of grass. More like a downstream reed but differs in that the fluid stream passes on both sides of the vibrating member.

By analogy of the generator to musical instruments (fig. 17), musical murmurs can be divided into 4 major varieties and a fifth mixed group: 1. The retroverted aortic cusp resembles the reed instruments in general principle but differs from all modern instruments of this type in the fact that the reed faces downstream not upstream. 2. Calcific aortic stenosis resembles the trumpeter's lip plus mouth-piece—a combination capable of generating musical tones (fig. 18). 3. Aberrant tendons of the ventricle resemble the Aeolian harp. 4. Rubbing pleuropericardial surfaces may, under some circumstances, resemble the violin group of instruments. 5. Certain musical peripheral vascular murmurs, some arterial, some venous, some probably arteriovenous, cannot be precisely analogized in this manner.

Examples of each type are presented. We have not studied the heart sounds in a patient proved to have aberrant tendon of the ventricle of the moderator band type, which Huchard described as a cause of musical murmur, but have found musical elements in the systolic murmur of ventricular septal defect. These may be produced by aberrant tricuspid chordae tendineae, which sometimes span the defect.

We have had a varied and interesting experience with musical murmurs that we believe are extracardiac in origin. Some of these, we think, fall in the group of murmurs just referred to by Dr. Harvey as "cardiac whoop." The features of this musical murmur (fig. 19) are as follows: (1) presumed innocence, judging from the usually healthy state of the subject; (2) late systolic timing; (3) association with a systolic click; (4) variation with respiration and with increased vigor of the heart beat—specifically accentuation with inspiration and following exertion or emotion; (5) development following pericarditis, such as the benign nonspecific variety; and (6) in some cases at least, the presence of mild pectus excavatum in the subject. The SPCG shows harmonics and the conventional PCG a regular periodic pattern at the rate of the fundamental. The evidence for extracardiac, specifically pleuropericardial, origin is (1) the clinical setting (point 5 above), (2) the association with systolic click (point 3) which from other evidence is judged to be of pleuropericardial origin in many instances,[26] and (3) the fact that the murmur may extend over the second heart sound slightly into diastole (cf. fig. 19).

In partial occlusion of arteries a continuous musical murmur in which the fundamental displays the pattern of an arterial pressure pulse may occur (fig. 20). (In other instances a more complex pattern is present.) Uterine souffle may show the same pattern.[27] Venous hums are occasionally musical (fig. 21). The mechanism of the musical murmur of partial arterial obstruction may be identical to that of the "musical murmur" of bronchial asthma, which in the sound spectrogram is characterized by harmonics[28]; the principle of Bernoulli,

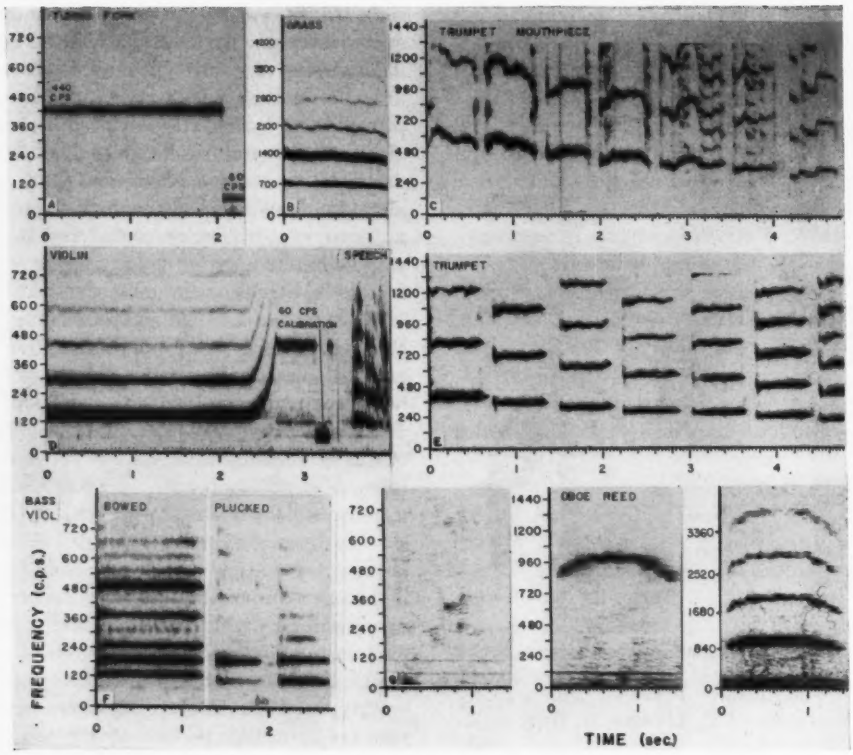

FIG. 18. *A*. Tone of 440 c.p.s. tuning fork and, on right, 60 c.p.s. calibration signal. *B*. Musical sound produced by blowing on a reed of grass. Note that the second harmonic is louder than the first, which is presumably the fundamental. This was also the situation in the case of the musical tone produced by a silk thread across a water-conducting tube.[25] *C*. Trumpet mouthpiece. The tones are not steady and impurities in the form of additional partials are present in certain notes. *D*. Violin with portamento (glide) from about 150 c.p.s. up to about 440 c.p.s. A brief segment of speech sound is also present and a 60-cycle calibration. *E*. Full trumpet. Here the tones are steady and pure. *F*. Musical sounds of a bass viol. *G*. Recording of musical sound produced by blowing on isolated oboe reed. These are analyses of the same sound on 3 different frequency scales. Below 720 c.p.s. there is nothing except wind noise. The fundamental, located at 960 cycles, appears in the analysis to 1,440 c.p.s. A total of 3 overtones is demonstrated in the third analysis.

as adapted to this situation by Rodbard, is probably operative. In general it appears that it is in the musical murmurs that Rodbard's "flitter" is most clearly involved as a mechanism; however, it seems to the speaker that to view these murmurs as a composite of a large number of closely timed transients is of doubtful usefulness although in a sense perhaps accurate.

Miscellaneous Auscultatory Phenomena. With inspiration not only may the diastolic murmur of tricuspid stenosis be greatly accentuated but also the interval between the second sound and the onset of the murmur is likely to be shortened. Increase in right atrial filling with inspiration is a satisfactory explanation.

Occasionally in patients with aortic stenosis and regurgitation one hears over the lower sternum a continuous machinery murmur simulating, in quality, that of patent ductus arteriosus, although the same patient demonstrates the usual double to-and-fro murmur in the aortic and pulmonary areas. The mechanism of the continuous murmur, which also in

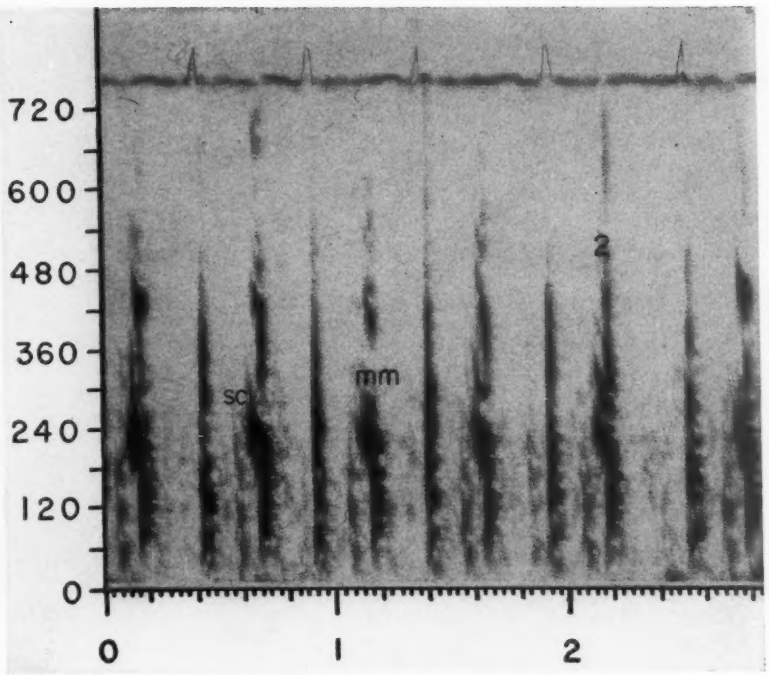

FIG. 19. Recorded at apex after exercise. It is noteworthy that there is a systolic click in the latter half of systole preceding the musical sound; therefore 2 phenomena, each of presumed extracardiac origin, are demonstrated.

the SPCG simulates that of patent ductus arteriosus, is unclear.

The murmur in one case of rupture of a sinus of Valsalva into the right atrium was continuous in character simulating patent ductus arteriosus on stethoscopy although in the phonocardiogram the intensity-frequency peak of the murmur was later than in patent ductus arteriosus. The murmur disappeared completely after successful surgical closure of the communication.

In a case of mitral obstruction due to left atrial myxoma the mitral first sound was snapping and moderately delayed ($Q\text{-}S_1 = 0.08$ second) and the pulmonic second sound was accentuated as in conventional mitral stenosis. A possible opening snap was present. Further phonocardiographic experience is necessary before it can be stated that the simulation of mitral stenosis by myxoma extends to the opening snap.

With ventricular septal defect the systolic murmur is likely to be holosystolic* when pulmonary hypertension is not present but becomes limited more and more to the earlier portion of systole as pulmonary hypertension progresses and may disappear entirely with severe degrees of pulmonary hypertension.

That a late systolic click may occur on the basis of pleuropericardial adhesion is suggested by its occurrence following clinical acute pericarditis, of rheumatic origin, for example. Clinical import derives from the possibility of mistaking the click and second sound for the second sound-opening snap combination of mitral stenosis.

* There is a tendency to use *pansystolic* and *holosystolic* interchangeably, to indicate a murmur filling the entirety of systole. It may be argued that holosystolic is preferable since pan- carries a connotation of "each." Pansystolic could mean a murmur occurring with each systole, whereas holosystolic can mean only a murmur filling systole.

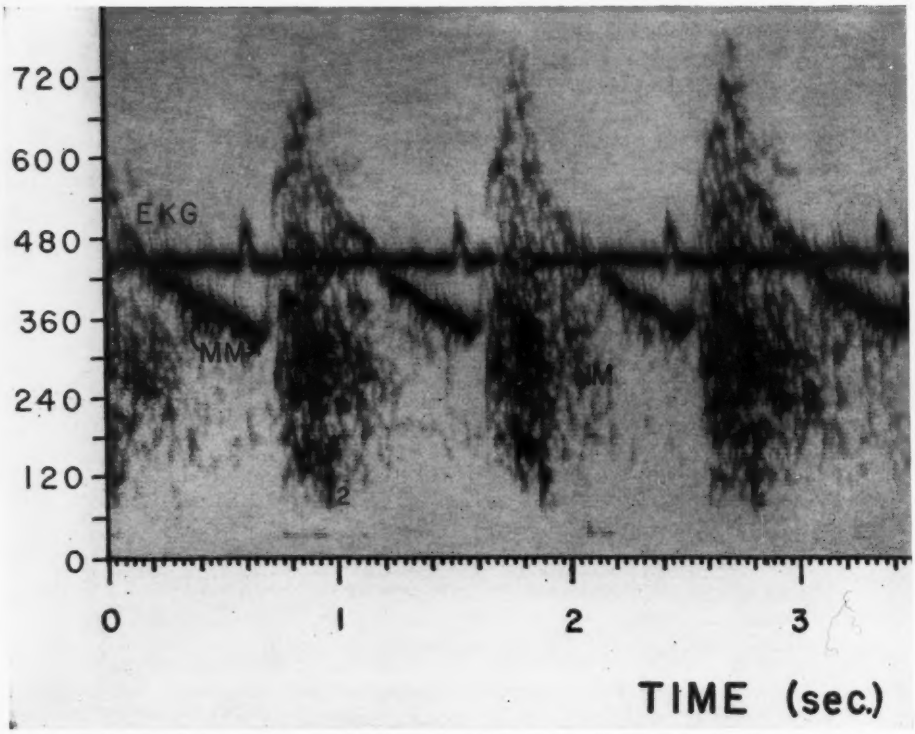

FIG. 20. Recorded over left carotid bifurcation. There is a noisy murmur with its peak at about the same time as the second heart sound which is faintly visible (*2*). There is a continuous pure tone with changeable frequency level describing an arterial pulse pressure curve. *MM*, musical murmur; *NM*, noisy murmur.

CLINICAL QUANTIFICATION OF THE INTENSITY OF HEART SOUNDS AND MURMURS: THE TRANSMISSION OF BASILAR SYSTOLIC MURMURS

EUGENE LEPESCHKIN, M.D., *Burlington, Vt.*

Quantification of Intensity. The introduction by Dr. Samuel Levine of a system of grading systolic murmurs according to their loudness has been helpful in the quantitative treatment of auscultatory phenomena. However, some confusion is still present due to the use of the original 6-grade system by some cardiologists and of a 4-grade system by others. Of the 62 cardiologists present at this meeting, 44 indicated that they use 6 grades, 8 that they use 4 grades, and 10 that they use no system of grading. Still, the identification of the grade of a given murmur is a highly individual process, and it would be of advantage to develop a more objective means of measurement. Ten years ago I built the first model of an attenuating stethoscope, in which the opening between the bell and earpieces could be gradually occluded until the murmur or heart sound could no longer be heard; the loudness of the murmur then corresponded to that of the audiometer sound, which could be just heard through the same opening. The instrument was perfected in 1950,[29] and through consultation with Dr. Levine it was found that each grade of his system corresponded to an increase in loudness of approximately 12 decibels.

However, the stethoscope had several disadvantages. The opening was so fine that it was easily plugged by dirt or moisture, and the clearance of the moving parts was so critical that the instrument could not be mass produced. Moreover, it could not attenuate sounds of an intensity more than 60 decibels because

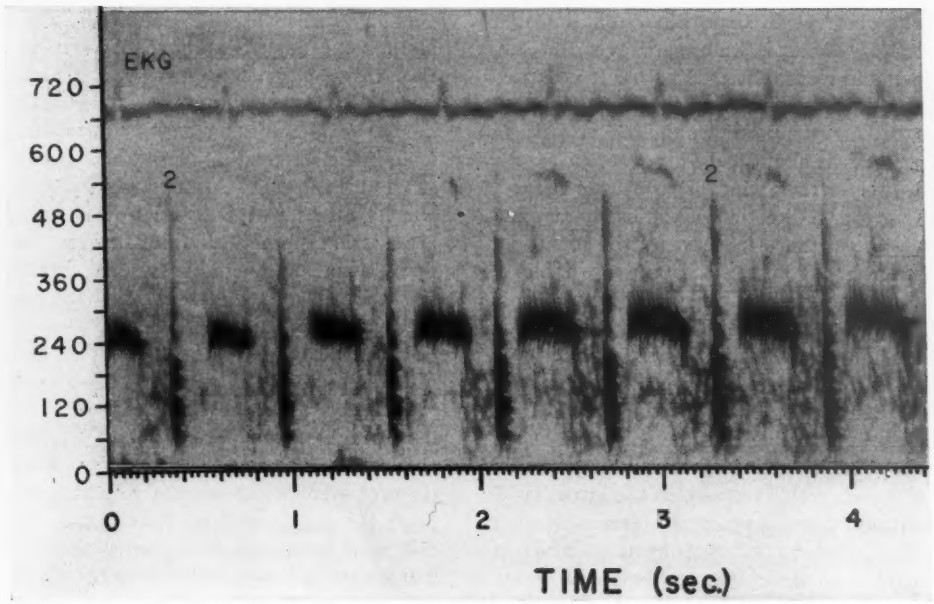

FIG. 21. Recorded at the base of the neck on the right, 17-year-old girl with coarctation of the aorta. A musical tone occurs consistently in late diastole. Owing to the hypertension the second sound is heard in the neck with unusual clarity. Note the gap between the second sound and the beginning of the musical murmur; this is evidence suggesting that venous flow is responsible for the murmur, since it might be expected that a gap of approximately this duration would be necessary for opening of the tricuspid valve and build-up of venous flow. For no apparent reason the musicality became louder, with slight rise in pitch, in the course of the recording. It also becomes longer by reason of beginning closer to the second sound. There would appear to have been an acceleration of venous flow.

the sounds of greater loudness were conducted through the wall even when the opening was closed. Finally, attenuation was always accompanied by a change in pitch. For these reasons, the amplifying electric stethoscope* was calibrated and modified to provide an amplification (or attenuation) of +15 to −100 decibels. This modified instrument avoids the disadvantages enumerated above, and, in addition, has the advantages of being able to amplify subthreshold murmurs and of eliminating the occasionally very disturbing sounds produced by rubbing of the stethoscope tubes against each other or the clothing of the listener.

The amplifying stethoscope we used has a peak sensitivity at about 500 c.p.s., similar to that of a binaural stethoscope with membrane chest piece, and it was calibrated at this frequency by means of a Western Electric audiometer. Measurements in normal persons showed that the loudness of the first heart sound ranges from 20 to 60 decibels at the point of maximal intensity, the loudness of the second heart sound ranges from 30 to 70 decibels at the aortic and 25 to 65 decibels at the pulmonic area, while the loudness of systolic murmurs ranges from −20 (inaudible range) to 40 decibels at the point of maximum intensity. Certain high-pitched, musical systolic murmurs may reach a loudness of 50 decibels. In general, persons overweight or those with pulmonary emphysema showed lower values for loudness than thin persons and children. Correlations with pulse pressure, blood viscosity and conductivity of the chest for a calibrating sound source are being made.

Propagation of Murmurs. One interpretation

* Maico Co., Minneapolis, Minn.

for the observation that the systolic murmur of aortic stenosis is well heard over the subclavian and carotid arteries is that it is carried by the blood stream, just as distant sounds may be carried by the wind. The velocity of sound in air is about 330 M. per second, and a moderately strong wind of 10 M. per second, blowing in the direction of the listener, would reduce the distance traveled by the sound per second by about 3 per cent. In the case of blood, however, the systolic velocity is at the most 0.4 M. per second while the sound velocity in water is around 1,400 M. per second, and this would lead to reduction of only 0.03 per cent in the distance traveled by the sound. It is therefore improbable that flow of blood in the direction of the point of auscultation should cause a measurable increase in the intensity of the murmur heard at this point. This conclusion was confirmed by an experiment in which a latex rubber T-drain was perfused with water and a point of stenosis was produced in the lower branch at its origin from the top section of the "T" (fig. 22). The clamps were adjusted so that the flow through the stenosis was equal to that past the stenosis. The intensity of the murmur was measured along the surface of the tube by means of the calibrated amplifying stethoscope described above. As can be seen from figure 21, the attenuation of the murmur is only 10 decibels within a distance of 10 cm. downstream from the stenosis, while upstream from it the attenuation is 70 decibels along the same distance. In this upstream section, in which water flows quietly past the stenosis, the attenuation is practically the same upstream or downstream, although the velocity of flow in this section is equal to that in the section downstream from the stenosis. The propagation of the murmur downstream from the stenosis with almost undiminished intensity can therefore not be due merely to the direction of the flow. The best explanation for this propagation is that the murmur is not conducted from the point of stenosis but actually recreated at each point of the tube wall by the vibrations in the disturbed flow pattern set up at the stenosis and continuing down the entire length of the tube.

In 5 cases of aortic stenosis, the average decrease in the intensity of the systolic murmur from the aortic area to the right carotid artery (a distance of about 20 cm.) was 15 decibels while the peak intensity showed a delay of 0.06 second (fig. 23). This corresponds to a conduction velocity of about 3.5 M. per second. A

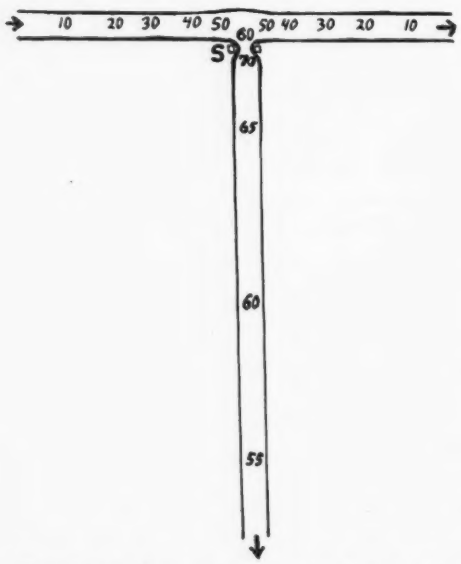

FIG. 22. Loudness of murmur, in decibels above hearing threshold, in the vicinity of a stenosis (*S*) in a perfused rubber tube. Direction of flow is indicated by arrows.

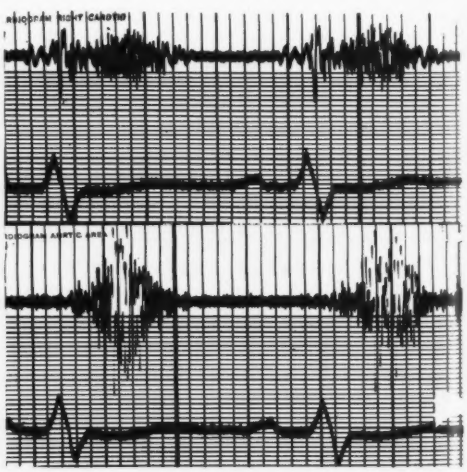

FIG. 23. Phonocardiogram of a patient with rheumatic aortic stenosis, demonstrating delay in the maximum of systolic murmur at the right carotid artery with respect to the aortic area.

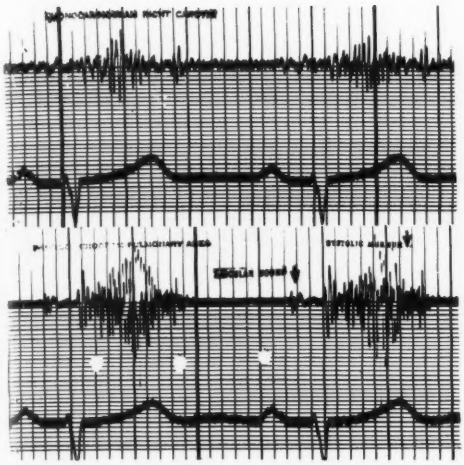

FIG. 24. Phonocardiogram of a patient with congenital pulmonary stenosis, showing synchronism of systolic murmur at the pulmonic area and the right carotid. The carotid tracing was taken at increased sensitivity.

similar average delay was found earlier by Kerr and Harp.[30] If the murmur were transmitted to the carotid artery by conduction at the speed of sound, the difference of intensity would have been much greater and no appreciable delay would have occurred, as in the case of a loud murmur of pulmonary stenosis (fig. 24). On the other hand, if the murmur were caused by the turbulent blood ejected through the stenosis arriving at the carotid artery, the delay would have been much greater. The speed of conduction of the murmur actually approximates that of the pulse wave, as previously suggested by Kerr and Harp.[30]

Discussion

DR. LEATHAM: In grading murmurs why not fractionate? One can say that a murmur is "grade 4 out of 6," written "4/6," or "grade 2 out of 4," and so on. There is then no confusion as to whether a base of 4 or 6 grades is used.

DIFFERENT TYPES OF DIAMOND-SHAPED BASAL SYSTOLIC MURMURS

CHRIST ARAVANIS, M.D., *Chicago, Ill.*

Seventy patients with loud aortic systolic murmurs were investigated by clinical, roentgenologic, and graphic means.

The tracing of the suprasternal notch, the carotid tracing, and the aortic kymogram presented data (slow rise, flat top or anacrotic notch, multiple vibrations) that were helpful in the differential diagnosis between obstructive stenosis and minor, nonobstructive aortic lesions, or relative aortic stenosis.

The study revealed that no statistical significance could be attached to the amplitude of the murmur and its distance from the first and second sound, or to the amplitude of the second aortic sound. The shape of the murmur, on the contrary, seemed important: 87.5 per cent of cases with relative stenosis had an early-diamond (i.e., early peak) and 66.7 per cent of cases with organic stenosis had a late-diamond (i.e., late peak). A late beginning and a late termination of the murmur, and a small, delayed second aortic sound are more often found in organic, obstructive valvular stenosis than in relative or nonobstructive stenosis.

Discussion

DR. DAVID H. LEWIS (*Philadelphia*): Am I correct in understanding that the differentiation of relative from organic aortic stenosis—on which this study was based—was made from the shape of the carotid pulse? I take it you do not have tracings of intra-arterial or aortic pressure.

DR. ARAVANIS: It has been demonstrated that the shape of the pulse in the substernal notch corresponds closely to that of the aortic pressure pulse. Furthermore, it has been demonstrated that the severer the aortic stenosis, the greater is the delay in the peak of the pulse wave.

HEART SOUNDS IN TOTAL ANOMALOUS PULMONARY VENOUS RETURN AND IN EBSTEIN'S ANOMALY

PATRICK A. ONGLEY, M.D., *Boston, Mass.*

Complete Transposition of the Pulmonary Veins. The general clinical picture associated with complete transposition of the pulmonary veins is well known. Pulmonary flow is much greater than normal and so murmurs due to increased flow through the great veins and through the tricuspid and pulmonic valves can be expected: (1) A systolic murmur over the pulmonic area; (2) a mid-diastolic–presystolic

murmur over the tricuspid area; and, (3) frequently a continuous murmur or venous hum over the great veins. There is often a third sound secondary to the increased early right ventricular filling and a fourth sound may result from increased force of right atrial contraction. With the rapid heart rates encountered in infants and children a summation gallop may result.

These characteristic sounds and murmurs have been encountered in those cases of complete transposition of the pulmonary veins in which drainage is into either the right or left superior vena cava, into the coronary sinus, or directly into the right atrium (fig. 25). We have not heard these murmurs when drainage has been below the diaphragm into the portal vein or the ductus venosus.

Ebstein's Anomaly. Ten cases of this anomaly have been studied clinically and during the past 5 years phonocardiograms have been recorded in 6 of them. The findings have been fairly consistent (fig. 26).

The first sound is of normal intensity and is best heard at the apex. The second heart sound is best heard at the lower left sternal border or at the apex and it is definitely diminished at the pulmonic area. In spite of a marked degree of right bundle-branch block the second sound was either narrowly split or unsplit in 3 of the patients and only normally split in 3 others. A prominent third sound was present in all patients. A fourth sound was occasionally present. In those patients with a short diastole the third and fourth sounds may be summated.

All patients showed a systolic murmur of moderate intensity, of medium frequency, and of either decrescendo or crescendo-decrescendo configuration. It was best recorded about the mid or lower left sternal border.

All patients showed a presystolic murmur which because of the prolonged P-R interval

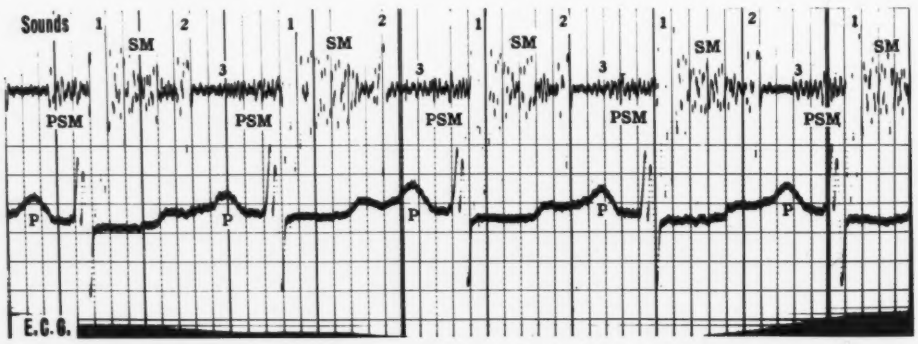

FIG. 25. Total anomalous pulmonary venous drainage. Prominent first sound (*1*); normal second sound (*2*); low-intensity third sound (*3*); medium frequency, moderate intensity, systolic murmur (*SM*); medium frequency, moderate intensity, presystolic murmur (*PSM*).

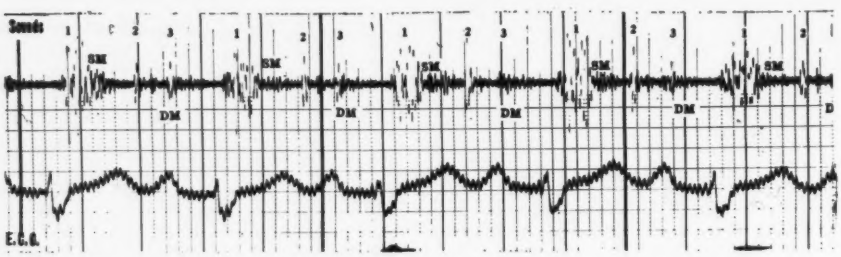

FIG. 26. Ebstein's anomaly. Prominent first sound (*1*); well split second sound (*2*); prominent third sound (*3*); decrescendo, medium frequency, moderate intensity, systolic murmur (*SM*); mid-diastolic murmur (*DM*), following the third sound, and the P wave of the electrocardiogram.

was not crescendic in quality. In some patients this murmur was quite intense and had a rather "scratchy" quality on ausculation.

Middiastolic murmurs at the apex were infrequently encountered and were of low intensity and medium to low frequency.

Discussion

DR. LUISADA: Was atrial septal defect present in these children?

DR. ONGLEY: Of course. All cases of total anomalous pulmonary venous return, to survive, must have a septal defect.

DR. LUISADA: And the Ebstein cases?

DR. ONGLEY: Some have an interatrial communication; some do not.

DR. LUISADA: The reason I ask is that in our cases of plain atrial septal defect 1 out of 3 or 4 showed a murmur in presystole completely separate from the first sound and usually recorded at the base in either the pulmonary or aortic area. We thought this murmur might be produced by the passage of blood through the defect.

DR. ONGLEY: We have felt that the murmur you refer to in atrial septal defect is tricuspid in origin. On catheterization the pressure differential between right atrium and right ventricle is more impressive than that between left atrium and right atrium.

DR. MCKUSICK: I have an isolated observation in total anomalous venous return and some observations on Ebstein's anomaly. This recording (fig. 27) is from a 21-year-old patient who for years was followed as probably having a patent ductus arteriosus, atypical in that the

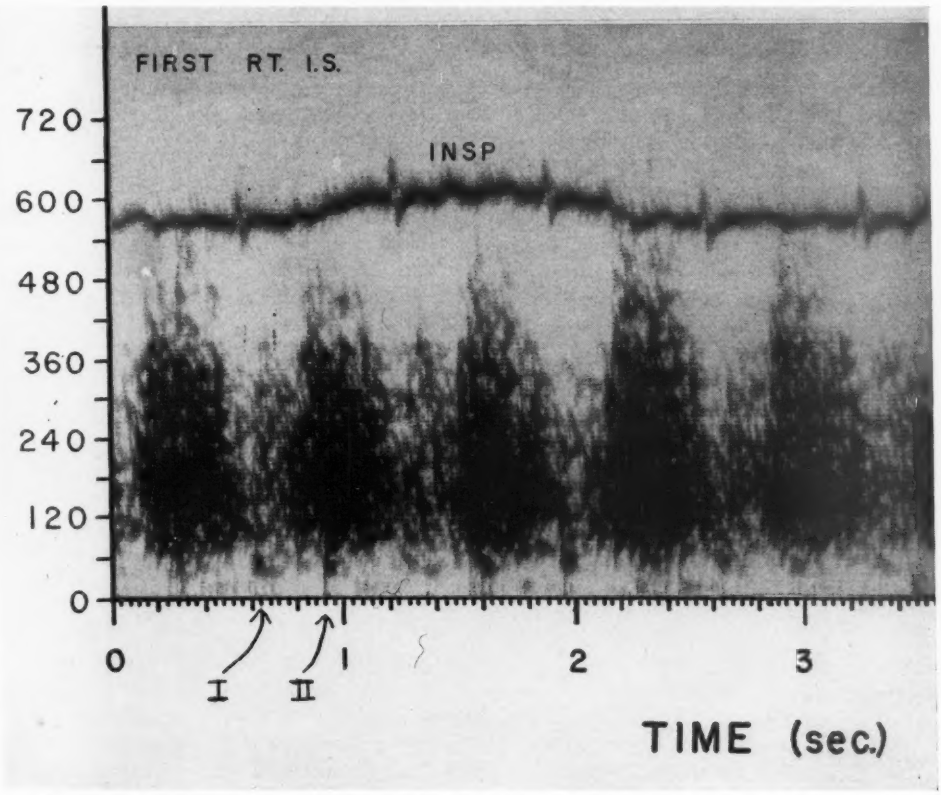

FIG. 27. Intense murmur has greatest amplitude and frequency span in the region of the second heart sound (*II*) as in the murmur of patent ductus arteriosus.[17] Recorded under midclavicle in first right interspace.

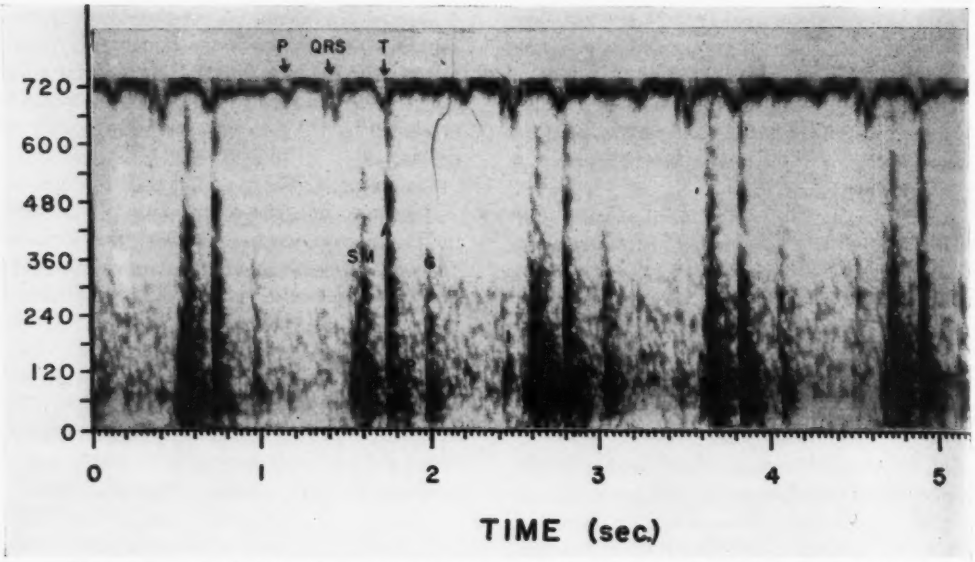

FIG. 28. Recorded in left midprecordium in 14-year-old boy with the clinical diagnosis of Ebstein's anomaly. Right bundle-branch block and prolonged P-R interval are present. The first sound (*1*) is faint. There is a midsystolic murmur (*SM*) with the configuration of a systolic ejection murmur. The second component of the split second sound, probably pulmonary closure (*P*), is diminutive relative to the first (*A*). A protodiastolic gallop (*G*) is present and probably initiates a short murmur.

murmur was maximal under the right clavicle, where this recording was made. The murmur was harsh and continuous, with none of the fickleness of a venous hum, and, in brief, with all the auscultatory features of patent ductus. Cardiac catheterization and angiocardiography have established the diagnosis of the "figure-eight," "cottage-loaf" or "snow-man" type of total anomalous venous return.

The striking gallop, occasionally double and resulting in quadruple rhythm, is the feature which has impressed us about the Ebstein cases. This feature seems quite characteristic and among patients with cyanotic heart disease immediately suggests this particular malformation to the stethoscopist. Midsystolic clicks also occur producing rather bizarre combinations. In the second place I am doubtful that tricuspid regurgitation accounts for the systolic murmur in all cases of the Ebstein anomaly. A circumscribed midsystolic murmur (fig. 28) with the shape of an ejection systolic murmur suggests that forward flow through the malformed tricuspid valve may be occurring. Blount[31] infers from intracardiac pressure patterns that the pretricuspid chamber contributes to propulsion of blood into the pulmonary artery.

CONCLUDING COMMENTS

FRANKLIN D. JOHNSTON, M.D., *Ann Arbor, Mich.*

I first became interested in sound records a great many years ago. As a matter of fact, the interest in sound records was the thing that originally got me into the Heart Station with Dr. Wilson, and I took a great many of them for a number of years. But about 10 years ago I had nearly decided that sound records were not worth doing, at least very often. Then Dr. Leatham and his associates in England, and other people, began to publish beautiful tracings, and not only publish the tracings but point out from these tracings the very interesting auscultatory findings that can be derived from them. As a matter of fact, and I think this is true of many other people in this country, our interest in sound tracings has been revived.

It is not the tracings themselves that are

really important; it is the things that they teach us. You see a few of these records and the next time you see a patient you are paying attention to the splitting of the first sound and the splitting of the second sound, and the chance of making a tentative clinical diagnosis of left branch block, let us say. I think that is the value of phonocardiography and I think it is wonderful.

Editorial Summary and Conclusions

No attempt will be made to summarize the numerous and interesting clinical observations that were reported in this part of the symposium.

In the concluding remarks Dr. Johnson emphasizes the educational value of phonocardiography. Its usefulness in 2 other respects should be indicated. 1. Inasmuch as phonocardiograms provide information that eludes the best-trained ear, they have scientific value. They permit precise time measurements and demonstrate sounds of low-frequency content beyond the perception of the ear. Other types of meaningful information may be provided by new methods, such as spectral phonocardiography, now under study. 2. Phonocardiography provides valuable documentation, particularly in cases of valvular heart disease, bearing on the course of disease and the effects of cardiac surgery. It keeps the clinician honest. Recently Dr. William Dock made the cogent statement: "We should no more think of sending a patient for valve surgery without a phonocardiogram than one would in the 'old days' think of sending a patient to Trudeau without a chest x-ray." Dock further stated in his Porter lecture[32]:

> The permanent objective records supplied by phonocardiograms are as valuable in managing heart disease as blood smears in leukemia, chest films in pulmonary tuberculosis, or electrocardiograms in coronary disease. Perhaps their greatest value is in teaching us to be better doctors at the bedside and in the office, and by making us less prone to error when the phonocardiogram is not available.
>
> Part of the advantage of objective documentation is the possibility of studying the records at leisure, and again and again. Ability to represent the auditory impression on the printed page is no mean aid to education and scientific progress.

The objective of phonocardiographic research should be to provide precision instruments and methods that can supplement, not merely embellish, the bedside diagnostic findings.

Summario in Interlingua

Non es essayate summarisar le multe e interessante observationes clinic reportate in iste parte del symposio.

In su remarcas conclusori, Dr. Johnson sublinea le valor pedagogic del phonocardiographia. Su utilitate ab 2 altere punctos de vista deberea esser signalate. (1) In tanto que phonocardiogrammas provide information que escappa al plus experte aure, illos possede valor scientific. Illos permitte precise mesurationes de tempore e demonstra sonos de frequentias infra le limine de perception per le aure. Altere typos de information significative va possibilemente esser obtenite per medio del nove methodos, per exemplo le phonocardiographia spectral, que es currentemente sub investigation. (2) Le phonocardiographia provide un documentation de valor—specialmente in casos de morbo de valvula cardiac—con respecto al curso del morbo e le effectos de chirurgia cardiac. Illo protege le honestitate del clinico. Recentemente Dr. William Dock faceva le pertinente constatation: "Nos debe tanto pauco pensar a inviar un patiente al chirurgia valvular sin un phonocardiogramma como in dies passate on haberea pensate a inviar un patiente a Davos sin un roentgenogramma thoracic." In su conferentia Porter, Dock diceva in plus[32]:

> Le permanente documentation objective providite per phonocardiogrammas es tanto utile in le tractamento de morbo cardiac como frottis de sanguine in leucemia, roentgenogrammas thoracic in tuberculose pulmonar, o electrocardiogrammas in morbo coronari. Le plus grande valor del phonocardiogrammas es forsan que illos insenia nos a esser melior medicos in le situation clinic e in le sala de consulta e que illos reduce le possibilitate de nostre committer errores quando phonocardiogramma non es disponibile.
>
> Un parte del avantage de un documentation objective es que on pote studiar lo deliberate e repetitemente. Le possibilitate de representar

le impression auditori in forma imprimite non es un detalio de negligibile adjuta in le instruction e in le progresso scientific.

Le objectivo de recercas phonocardiographic deberea esser le provision de instrumentos de precision e de methodos exacte que servi a supplementar e non solmente a adornar le constatationes diagnostic del clinico.

ACKNOWLEDGMENT

In preparing the written form of this symposium, the editor, Dr. McKusick, had the assistance of Drs. S. H. Boyer IV, Robert P. Grant, Hans H. Hecht, J. O'Neal Humphries, Andrew Kerr, Jr., Simon Rodbard, Robert F. Rushmer, and Samuel A. Talbot.

REFERENCES

[1] KERR, A., JR., AND PALMER, E. D.: The Balthazar Foster murmur and Foster's rule. New England J. Med. **248:** 1064, 1953.

[2] DOCK, W.: Mode of production of the first heart sound. Arch. Int. Med. **51:** 737, 1933.

[3] BRAUNWALD, E., FISHMAN, A. P., AND COURNAND, A.: Time relationship of dynamic events in the cardiac chambers, pulmonary artery and aorta in man. Circulation Research **4:** 100, 1956.

[4] LEATHAM, A.: The phonocardiogram of aortic stenosis. Brit. Heart J. **13:** 135, 1951.

[5] —: Phonocardiography. Brit. M. Bull. **8:** 333, 1952.

[6] — AND VOGELPOEL, L.: The early systolic sound in dilatation of the pulmonary artery. Brit. Heart J. **16:** 21, 1952.

[7] — AND WEITZMAN, D. W.: Auscultatory and phonocardiographic signs of pulmonary stenosis. Brit. Heart J. In press.

[8] — AND GRAY, I.: Auscultatory and phonocardiographic signs of atrial septal defect. Brit. Heart J. **18:** 193, 1956.

[9] WOLFERTH, C. C., AND MARGOLIES, A.: Asynchronism in contraction of the ventricles in the so-called common type of bundle-branch block: its bearing on the determination of the side of the significant lesion and on the mechanism of the split first and second heart sounds. Am. Heart J. **10:** 425, 1935.

[10] LEATHAM, A.: A classification of systolic murmurs. Brit. Heart J. **17:** 574, 1955.

[11] —: Splitting of the first and second heart sounds. Lancet **11:** 607, 1954.

[12] GRAY, I. R.: Paradoxical splitting of second sound. Brit. Heart J. **18:** 21, 1956.

[13] CONTRO, S., AND LUISADA, A. A.: Modifications of the heart sounds in bundle branch block. J. Mt. Sinai Hosp. **19:** 70, 1952.

[14] BRAUNWALD, E.: Personal communication.

[15] BRAUNSTEIN, E., AND MORROW, A. G.: The sequence of ventricular contraction in bundle-branch block. Presented at meeting of American Heart Association, Cincinnati, Oct. 28, 1956. Abstracted, Circulation **14:** 915, 1956.

[16] MCKUSICK, V. A., REAGAN, D. P., SANTOS, G. W., AND WEBB, G. N.: The splitting of heart sounds. Am. J. Med. **19:** 849, 1955.

[17] —, MASSENGALE, O. N., JR., WIGOD, M., AND WEBB, G. N.: Spectral phonocardiographic studies in congenital heart disease. Brit. Heart J. **18:** 403, 1956.

[18] MOUNSEY, P.: The opening snap of mitral stenosis. Brit. Heart J. **15:** 135, 1953.

[19] WOLTER, H. H., BAYER, O., AND QUERRMAN, I.: Zur Beurteilung des Schwergrades von Mitralstenosen. Ztschr. Kreislaufforsch. **44:** 177, 1955.

[20] SHULER, R. H., ENSOR, C., GUNNING, R. E., MOSS, W. G., AND JOHNSON, V.: Differential effects of respiration on the left and right ventricles. Am. J. Physiol. **137:** 620, 1942.

[21] SCHOELMERICH, P., AND GEHL, H.: Herzschallstudien beim Lagewechsel. Ztschr. Kreislaufforsch. **40:** 211, 1951.

[22] —: Zur Differentialdiagnose und Theorie der Ueberzaehligen Herztoene. Verhandl. deutsch. ges. Kreislaufforsch. **17:** 227, 1951.

[23] MCKUSICK, V. A., WEBB, G. N., HUMPHRIES, J. O'N., AND REID, J. A.: On cardiovascular sound. Further observations by means of spectral phonocardiography. Circulation **11:** 849, 1955.

[24] —, —, BRAYSHAW, J. R., AND TALBOT, S. A.: Spectral phonocardiography: Clinical studies. Bull. Johns Hopkins Hosp. **95:** 90, 1954.

[25] —, MURRAY, G. E., PEELER, R. G., AND WEBB, G. N.: Musical murmurs. Bull. Johns Hopkins Hosp. **97:** 136, 1955.

[26] REID, J. A., AND HUMPHRIES, J. O'N.: Systolic clicks (so-called systolic gallops): A study of their clinical significance. Bull. Johns Hopkins Hosp. **97:** 177, 1955.

[27] MCKUSICK, V. A., KLINE, E. W., AND WEBB, G. N.: Spectral phonocardiographic demonstrations of selected varieties of cardiovascular sounds. Am. Heart J. **49:** 911, 1955.

[28] —, JENKINS, J. T., AND WEBB, G. N.: The acoustical basis of the chest examination. Studies by means of sound spectrography. Am. Rev. Tuberc. **72:** 12, 1955.

[29] LEPESCHKIN, E.: A quantitative stethoscope and its clinical applications. Am. Heart J. **43:** 881, 1952.

[30] KERR, W. J., AND HARP, V. C., JR.: Transmission of murmurs. Am. Heart J. **37:** 100, 1949.

[31] BLOUNT, S. G., JR., MCCORD, M. C., AND GELB, I. J.: Ebstein's anomaly. Circulation **15:** 210, 1957.

[32] DOCK, W.: Heart Sounds, Cardiac Pulsations, and Coronary Disease (Porter Lectures). Lawrence, University of Kansas Press, 1956, p. 64.

CLINICAL PROGRESS

Fluid and Electrolyte Disturbances in Heart Failure and their Treatment

By CHARLES K. FRIEDBERG, M.D.

ADVANCES in our understanding of fluid and electrolyte disturbances in congestive heart failure have at the same time increased our therapeutic effectiveness and engendered new problems and new complications related to our more vigorous therapy. The physician who treats patients with heart failure should be cognizant both of the advantages and dangers associated with these developments. The purpose of this presentation is both to delineate the current status of our knowledge of fluid and electrolyte disturbances in heart failure and to translate this knowledge, obtained largely by laboratory technics, to its practical application at the bedside.

BODY WATER AND FLUID COMPARTMENTS

Although there is free intercommunication of all body water, the cell membranes have anatomically segregated water within the cells (intracellular fluid) from that outside the cells (extracellular fluid). Furthermore, the walls of blood vessels have further subdivided extracellular water into that within the blood vessels, plasma, from that outside—interstitial fluid. These subdivisions of body water are conceived as forming distinct compartments not only because of anatomic separation, but because the fluid in the various compartments differs in its chemical content and in its physiologic behavior.

Measurement of Body Water Compartments

The quantity of fluid in a given compartment is measured by determining the degree of dilution of an injected substance that distributes itself homogeneously throughout the given compartment within a relatively brief period of time.[1] The injected substance must remain exclusively within the compartment during the test period, or the amount leaving the compartment must be determinable. The volume of the fluid compartment that is being measured is calculated as the amount of substance injected (less any that was eliminated from the compartment, e.g., excreted in the urine during the test period), divided by the concentration of the test substance in the plasma at the end of the test period.

Antipyrine, deuterium oxide, or tritium,[2] which is rapidly distributed throughout all the water in all compartments following intravenous injection, is used to measure total body water. Inulin or sucrose, nonmetabolized, diffusible carbohydrates, which become distributed throughout plasma and the interstitial tissue but do not enter cells, may be used to measure the extracellular fluid volume.[3] Bromide, chloride, radiosodium, and sodium thiocyanate, formerly used to measure the extracellular fluid volume, are known to enter cells and connective tissue to a limited degree and therefore yield higher values than inulin or sucrose. The Evans blue dye, T 1824, is promptly bound to plasma albumin after intravenous injection, mixes homogeneously, and remains confined to the intravascular compartment long enough to be used as a measure of the plasma volume. Similarly, radioiodinated serum albumin[4] or radioactive chromic chloride[5] may be used to measure plasma volume. The red cell volume can be measured by injecting radioactive chromium. The hematocrit is determined and the plasma is calculated from these 2 values. However an error is introduced because the venous blood hematocrit, as usually performed, is less than that of the over-all body hematocrit. The intracellular fluid volume is not measured directly, but may be

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TABLE 1.—*Body Water in Man Weighing 75 Kg.*

Compartment	Liters	Per cent body weight
Plasma volume	3.4	4.5
Interstitial volume	9.4	12.5
Extracellular volume	12.8	17.0
Cell (intracellular) volume	32.2	43.0
Total body water	45.0	60.0

calculated by subtracting the determined extracellular fluid volume from the determined total body water. Similarly, the volume of interstitial fluid can be calculated by subtracting the plasma volume from the extracellular volume.

Normal Body Water Values

The quantity of total body water bears an almost constant relationship to the lean (fat-free) body weight of approximately 70 per cent (table 1). This ratio diminishes with increasing stores of fat. In adult, nonobese men, total body water is approximately 60 per cent and in women 50 per cent of body weight.

The extracellular fluid volume measures about 17 per cent of body weight with inulin or sucrose, and between 25 and 35 per cent when determined by chloride or thiocyanate. If the extracellular fluid is regarded as amounting to approximately 20 per cent of body weight, then one quarter of this, or 5 per cent of body weight, represents the plasma volume and 15 per cent the interstitial fluid.

ELECTROLYTES: MEASUREMENT AND DISTRIBUTION

The integrity of the living cell depends on the maintenance of a normal, relatively unchanging osmotic pressure of the cellular and extracellular fluid. The osmotic pressure, in turn, is dependent upon the concentration of dissolved ions (electrolytes). The concentration of electrolytes is controlled and osmotic equilibrium is maintained, at least in part, by the free passage of water into and out of cells and other fluid compartments. Alterations in osmotic pressure resulting from changes in electrolyte concentration are usually rapidly restored to normal by the passage of fluid into or out of cells and by a cellular-extracellular transfer of ions.

Electrolyte Concentrations, Milliequivalents

The major cations are sodium in the extracellular fluid and potassium in the intracellular fluid, while the chief anions are chloride and bicarbonate in the extracellular fluid and phosphate, sulfate, bicarbonate, and protein in the intracellular fluid. Since electroneutrality is preserved in all the body fluid compartments, the sums of positive and of negative charges are equal in number. Therefore, it is preferable to state the concentration of body electrolytes in terms of equivalents rather than of weight. An equivalent is the amount of substance that will react with or replace a gram atomic weight of hydrogen. Body electrolytes are usually measured in terms of the milliequivalent (mEq.), which is one thousandth of an equivalent. The number of milliequivalents of an electrolyte is calculated from its weight by first dividing the number of milligrams of that electrolyte by its atomic weight, and then multiplying by the valence of the electrolyte concerned.

Thus 156 mg. of K (atomic weight 39, valence 1) equal 4 mEq., viz. $(156/39) \times 1 = 4$. Similarly, 142 mg. of Cl^- (atomic weight 35.5) equal 4 mEq., viz. $(142/35.5) \times 1 = 4$. Although differing in weight, 156 mg. of K (4 mEq.) combine with 142 mg. of Cl^- (4 mEq.). Furthermore, the resulting 298 mg. of KCl is also equal to 4 mEq. or rather 4 millimolecules or millimols (mM) of KCl; the number of milligrams divided by the molecular weight, viz. $298/74.5 = 4$. It is of practical value to remember that 1 Gm. (1000 mg.) of potassium chloride equals 13.4 mM of KCl, and 13.4 mEq. each of potassium and chloride, viz. $1000/74.5 = 13.4$. Similarly, 1 Gm. (1000 mg.) of sodium chloride equals 17.1 mM, and 17.1 mEq. each of sodium and chloride. With respect to Ca, which has an atomic weight of 40 and a valence of 2, 100 mg. represents 5 mEq., viz. $(100/40) \times 2 = 5$. To convert milliequivalents to milligrams, one divides by the valence and multiplies by the atomic weight, e.g., 4 mEq. of calcium equals 4 divided by $2 \times 40 = 80$ mg.

The concentration of electrolytes in body fluids is usually expressed in terms of milliequivalents per liter. When, however, it is stated in terms of milligrams per 100 ml. the latter may be converted to milliequivalents per liter by multiplying the number of milligrams by 10 (i.e. 1000 ml.) before making the above conversion from milligrams to milliequivalents. The plasma carbon dioxide is often expressed in terms of volumes per cent (i.e., per 100 ml.). To convert from volumes per cent of carbon dioxide to millimols per liter, the number of volumes per cent is multiplied by 10 and the product is divided by 22.4. The latter represents the number of liters of gas occupied by a mole. Conversely, to convert millimols of carbon dioxide to volumes per cent, one divides by 10 and multiplies by 22.4. Thus 56.2 vol. per cent of carbon dioxide = 56.2 × 10 divided by 22.4 equals 25 mM per L.

Measurement by Flame Photometer

A knowledge of body electrolytes requires the determination of both the concentration of the electrolytes in the different fluid compartments and the total quantity of body electrolytes. The concentration of electrolytes in the plasma, as well as in the total extracellular fluid of which the plasma is representative, is determined by means of the flame photometer. So many of our recent advances in the field of electrolytes are due to the ease and speed of measuring sodium and potassium concentrations by the flame photometer that a brief description is indicated. A unit of serum, urine, or other body fluid, is diluted to 1:50, 1:200, or as desired. The diluted fluid is poured into a funnel that leads to a vaporizer controlled by a constant air pressure. The solution is thus vaporized into a flame, which is largely enclosed within the apparatus and which is maintained constant by a constant gas pressure and supply of air. The sodium ion imparts a yellow, and potassium a purple color to the flame, the color intensity being proportional to the concentration of the electrolyte. This color is transmitted through appropriate filters to a photoelectric cell and thus produces a current whose intensity is proportional to the intensity of the color in the flame and therefore to the concentration of the electrolyte. This current is measured by a galvanometer. The concentration of the electrolyte is then determined by comparison of the current produced by the unknown solution with that produced by known concentrations of sodium or potassium. In practice, 10 per cent lithium is added to the control and to the unknown solutions. The lithium produces its own color and current. This then acts as an internal standard. One measures the resistance necessary to equalize the current produced by the unknown solution with the current produced by the constant lithium solution. Similar measurements are made with control solutions (standards) containing known amounts of the electrolyte to be determined.

Total Plasma and Extracellular Electrolytes

The total plasma content of a given electrolyte or the total amount of that electrolyte in the extracellular fluid is determined by multiplying the concentration in the plasma by the quantity of plasma or by the quantity of extracellular fluid respectively, as determined above.

Measurement of Total Exchangeable Sodium and Potassium

The total exchangeable body sodium or potassium, i.e., intracellular as well as extracellular, can be determined by injecting radioisotopes Na^{24} or Na^{22} or K^{42} and utilizing the principle of dilution. For example, a known amount of radiosodium is injected intravenously and the concentration of radioactive sodium and of stable sodium ion in the plasma is determined after a period of equilibration, usually 24 hours later. The total exchangeable sodium is calculated by dividing the total counts per minute of radiosodium retained in the body at the time of sample collection, by the specific activity, which is the ratio of the radioactive sodium to stable sodium concentration in the plasma.

Normal Values of Total Exchangeable Sodium and Potassium

The average amount of total exchangeable sodium measured by Na^{24} dilution is approximately 40 mEq. per Kg. body weight.[6] In a man weighing 75 Kg., there would be a total

exchangeable sodium of 3000 mEq. If the extracellular water is taken to be 20 per cent of body weight, or 15 L. in this example, and if 140 mEq. per L. is the normal concentration of sodium in the extracellular fluid, then the total amount of sodium in the extracellular fluid would be 15 × 140 or 2100 mEq. Of the remaining 900 mEq. of exchangeable sodium, about 300 mEq. are within the cells and the remaining 600 mEq. represent the exchangeable portion of sodium found within bone. The total exchangeable sodium represents only about 68 per cent of total body sodium.[7] Analysis of adult male carcasses revealed a sodium concentration of 62 mEq. per Kg. body weight, while isotopic dilution revealed a sodium concentration of 42 mEq. per Kg. body weight.[8] Direct measurements have indicated that total bone sodium represents 30 per cent of total body sodium. Of this about 45 per cent is exchangeable.[9] There is evidence that in various conditions of sodium depletion the bone represents a reservoir of sodium[10] that is made available for the body fluids and, conversely, in conditions with abnormal sodium retention, some of the excess sodium may be stored in bone.

The total body exchangeable potassium averages about 45 mEq. per Kg. body weight, somewhat more in males and somewhat less in females. In a man weighing 75 Kg. the total exchangeable potassium amounts to approximately 3375 mEq. Since the concentration of potassium in extracellular fluid is about 4.5 mEq. per L., and since there are about 15 L. of extracellular fluid in the example mentioned, the total amount of extracellular potassium would be 15 × 4.5 or 67.5 mEq. It is apparent that approximately 3300 mEq. of the total exchangeable potassium is within the intracellular phase. Because of the predominant intracellular location of potassium, considerable body depletion of potassium may exist, without an apparent or significant change in its plasma concentration.

Measurement of Intracellular Electrolytes

The concentration of intracellular electrolytes is difficult to determine accurately. Some of the data have been attained by direct analysis of muscle obtained by biopsy. This method is hampered by the presence of extracellular fluid included in the muscle specimen. The amount of exchangeable intracellular sodium and potassium can be calculated by subtracting from the total exchangeable sodium or potassium in the body the amount in the extracellular fluid as determined above. Because the quantity of one or the other electrolytes predominates so greatly, either in the extracellular or intracellular compartment, there is considerable error in using this method of subtraction.

Normal Values of Extracellular and Intracellular Electrolytes

The average normal concentrations of the most important electrolytes and the total quantities in the body in the various fluid compartments are listed (tables 2 and 3).

The concentrations of the major cations and anions differ in the extracellular and intracellular compartments because of differences in permeabilities of the cellular and vascular membranes to the passage of organic and inorganic solutes. Differences in the concentration of electrolytes within and outside cells are due to ion-transfer mechanisms within the cells that control the quantities of electrolytes entering and leaving the cell. By these mechanisms,

TABLE 2.—*Plasma Electrolyte Concentrations*

Cations (mEq./L.)		Anions (mEq./L.)	
Na	143	Cl	103
K	4.5	HCO_3	27
Ca	5.5	PO_4	2.5
Mg	2.0	SO_4	0.5
		Organic acids	6.0
		Protein	16.0
Total	155.		155.

TABLE 3.—*Electrolyte Concentrations in Interstitial and Intracellular Fluid*

	Interstitial fluid mEq./L.	Intracellular fluid mEq./L.
Na	138	37
K	5	112
Cl	109	25
HCO_3	28	10 (?)

which utilize cellular enzymes and cellular energy, sodium and chloride enter the cell to a limited extent, even though there is a much higher concentration of these ions outside than inside the cell.[12-14] Similarly, cellular potassium leaves the cell for the extracellular fluid only to a limited extent, despite the higher cell concentration. Under a variety of circumstances extracellular potassium enters cells against the concentration gradient.

The concentration of electrolytes in interstitial fluid is very similar to that of plasma, with slight variations related to the Donnan equilibrium. This difference results from the fact that 10 per cent of the anions in plasma are formed by nondiffusible, negatively charged proteins, which are present only to a minimal degree in the interstitial fluid. Consequently the sodium concentration in the interstitial fluid is about 5 per cent lower and that of chloride about 5 per cent higher than in plasma. In addition, the concentration of calcium in interstitial fluid is about half that of plasma because only half of the plasma calcium is diffusible.

Body Water in Congestive Heart Failure

Total Body Water in Heart Failure

Although heart failure is fundamentally related to sodium retention, the symptoms and signs of congestive heart failure are more directly due to an increase in the quantity and abnormal localization of body water. That congestive heart failure is associated with a marked increase in total body water is readily demonstrable by gross clinical observation, particularly when the heart failure is severe. The increase in body water is indicated by a sharp rise in body weight within a matter of days or a few weeks, exceeding in quantity any rise that could be attributed to an augmented caloric intake. In fact, the rapid rise in weight often occurs despite a reduction in food intake. Second, and often more striking, the administration of a mercurial diuretic may be followed by a weight loss of 1 to 5 Kg. or more within 24 hours. Furthermore, there is usually a concomitant alleviation of the symptoms of heart failure. The rapidity and magnitude of the fluctuation in weight indicate that these changes are due to gain or loss of water respectively. The appearance or intensification of symptoms with weight gain and their prompt relief with diuresis and weight loss indicates that these symptoms are determined by the abnormal water retention.

The correlation of symptoms with water retention is not readily apparent in most cases of early heart failure or, more specifically, pure left heart failure, even when the symptoms are severe. This dissociation may be due to the imperfection or inaccuracy of available methods for measuring pulmonary or intrathoracic body water. Nevertheless in left heart failure, symptoms and signs are attributed to pulmonary congestion and, when severe, to pulmonary edema. Although no sharp weight gain may be demonstrable with the development of symptoms of left heart failure and no striking weight loss with their alleviation, the exhibition of a mercurial diuretic with even a moderate diuresis is usually followed by unequivocal symptomatic improvement.

Although the total body water in heart failure can be determined by the injection of deuterium oxide or antipyrine,[15] this dilution technic is cumbersome and may be inaccurate because of the long period required for mixing and the difficulty of obtaining homogeneous diffusion of the injected material in the presence of edema or serous effusions. Hence clinical observations of rapid change in body weight are more practical and probably yield more accurate estimates of alterations in total body water.

Intracellular Fluid

There is uncertainty whether any of the increased total body water in heart failure is intracellular. Electrolyte and water balance studies during the recovery from heart failure suggest that there is an increase in intracellular as well as extracellular water. In subjects recovering from heart failure, balance studies showed that sodium loss was much less than that to be anticipated from the loss of body water and body weight.[16] In such patients, also, the ratio of sodium to water in urine is less

than that in serum, i.e., water is excreted in excess of sodium.[17, 18] The decrease in body weight following intensive diuretic therapy was noted to be too great to be related solely to a reduction in Na^{24} space or exchangeable sodium.[19] From these observations it has been concluded that water loss during recovery from heart failure comes from the intracellular as well as the extracellular compartment. On the other hand, dilution studies with antipyrine and radioisotopic sodium (Na^{24}) were interpreted as indicating a loss of intracellular water and a gain of extracellular water in edematous patients with heart failure.[20] Furthermore, there was a greater retention of total sodium than total body water during heart failure, even though a disproportionately greater amount of water than sodium is excreted during the early stages of diuresis and recovery.

The relatively few determinations of intracellular water by subtraction of extracellular from total body water have not given consistent results. The inaccuracies of determining both total and extracellular water in congestive heart failure apply equally to the calculation of intracellular water from these values. A study of intracellular water in skeletal muscle biopsies indicated that the increase in muscle water in heart failure was due entirely to augmented extracellular volume without significant alteration in intracellular water.[21]

Extracellular Fluid in Heart Failure

The major portion, if not the entire amount, of excess body water in congestive heart failure is situated within the extracellular space. This increase is most apparent in advanced heart failure, which is characterized by the presence of edema and serous effusions. The edema fluid and effusions represent body water that is extracellular but also outside the blood vessels. Few direct measurements of the extracellular fluid have been made. Direct measurements of extracellular fluid like those of total body water are hampered by delayed and nonuniform mixing of the injected test substances in cases of heart failure with considerable edema. In one series of cases, extracellular fluid, determined as the volume of distribution of inulin, was 14.1 per cent of body weight in 4 noncardiac controls and 24.5, 27.8, and 36.6 per cent of body weight, respectively, in 3 cardiac patients with heart failure and varying amounts of edema, but without serous effusions.[21] In another series of 5 patients with congestive heart failure, the inulin space ranged from 18.5 to 39.4 per cent of body weight corresponding to increasing degrees of edema, whereas in normal controls the inulin space averaged 16.2 per cent of body weight.[22] In a series of patients with mild congestive heart failure there was an average increase of 5 L. of extracellular fluid over control values, as determined by isotope-dilution studies, despite the absence of overt edema.[23]

Available studies indicate that, in the presence of frank edema, the extracellular fluid is usually at least twice its normal volume. In an adult male weighing 75 Kg., whose extracellular fluid represents 17 per cent of body weight, there would be approximately 12.8 L. of extracellular fluid normally. There may be no visible edema when the latter is increased to 17 L., i.e., when the increased extracellular fluid weighs 4.2 Kg. or 9 lb. When the extracellular fluid is doubled, as occurs in severe heart failure with edema, the excess extracellular fluid in the example cited weighs 12.8 Kg., or 28 lb. This amount of edema is not uncommonly lost by a patient when he recovers from severe heart failure.

Blood Plasma Volume in Heart Failure

The general belief that the plasma volume is increased in heart failure has been disputed by several observers in recent years. Nevertheless the weight of evidence strongly indicates that the plasma volume is increased and tends to return to normal when heart failure is controlled.[24, 25] But the degree of increase is in no way comparable to that of the interstitial portion of the extracellular fluid and usually amounts to 15 to 50 per cent above normal. If the plasma volume of a normal man weighing 75 Kg. is 3.5 L., the plasma volume in heart failure might be 5 L., an increase of only 1.5 L., whereas the interstitial fluid volume in such a patient with heart failure is frequently of the order of 20 L. instead of a normal of 10 L. Despite a massive increase in extracellular fluid

volume, the plasma portion of the extracellular volume is maintained at a relatively more stable level than that of the interstitial fluid.

It is apparent that the simple transudation of the plasma volume cannot account for the increase in interstitial fluid because increase in the latter often exceeds the total plasma volume. Since the increased interstitial fluid is effected by transfer from the plasma, other mechanisms must be tending to increase the plasma volume as rapidly as, or more rapidly than, plasma water leaves the blood stream for the intercellular spaces. This process denotes a positive water balance during the progress of congestive heart failure, whereby the excretion of water by the kidney and other routes of external water loss is less than the quantity of water ingested. The positive water balance is due chiefly to a diminished glomerular filtration and excessive renal tubular reabsorption of water. Renal retention of water tends to increase the circulating blood volume. This increase diminishes the concentration of serum albumin and the colloid osmotic pressure, which serves to retain water within the blood vessels. At the same time the increased capillary pressure in heart failure causes transudation of the increased plasma water into the extracellular spaces.

Electrolytes in Congestive Heart Failure

Abnormal Sodium Retention

Although the clinical features of congestive heart failure are largely the result of abnormal retention and distribution of water, the water retention is generally regarded as being secondary to an abnormal renal retention of sodium. The evidence for this belief is direct and unmistakable. The patient whose heart failure has been greatly alleviated will rapidly develop edema and experience a recurrence of symptoms if he resumes a liberal salt intake. Conversely, restriction of salt, per se, frequently induces relief of symptoms and a loss of fluid or permits a favorable response to digitalis and mercurial diuretics.

That it is salt and not water intake that is primarily responsible for the edema and intensification of symptoms is indicated by the observation that the benefits of salt restriction are obtained even when water intake is unrestricted. In fact, in many patients with heart failure, fluid intakes of 2 to 3 L. are associated with a greater loss of retained water than smaller fluid intakes, provided that the sodium intake is adequately restricted. Conversely, restriction of fluid intake is generally ineffective if a liberal salt intake is permitted.

A more direct demonstration of abnormal salt retention is provided by observations of sodium excretion following the rapid intravenous administration of hypertonic sodium chloride in patients with heart failure. In the normal individual following the intravenous administration of 25 Gm. (428 mEq.) of sodium chloride as a 5 per cent solution, about 20 per cent of the administered sodium is excreted in 2 hours and 60 per cent in 20 hours, whereas, in the patient with congestive heart failure, only 2.5 per cent may be excreted in the first 2 hours and only 8 per cent after 20 hours.[26]

The deleterious effects of sodium chloride in congestive heart failure and the abnormal retention of sodium chloride are applicable to the sodium and not to the chloride ion. Similar effects are induced by the oral or parenteral administration of other sodium salts such as sodium bicarbonate or sodium lactate. On the other hand, chloride salts without the sodium ion have no such effect. In fact, as is well known, ammonium chloride promotes the excretion of sodium and may act as a diuretic.

The degree of deficiency in renal excretion of sodium varies considerably in patients with congestive heart failure according to the severity of the heart failure. With heart failure of relatively mild degree, sodium retention occurs only with unusually large sodium loads. Therefore, in some patients with minimal heart failure a relatively liberal sodium intake of 5 to 10 Gm. of sodium chloride distributed over a day may be entirely excreted within the day, causing no abnormal retention of sodium or fluids. In the same patients a daily intake of 10 to 15 Gm. of sodium chloride may cause sodium and water retention and overt symptoms. Thus, although there is a diminished reserve with respect to sodium excretion, the kidney is capable of excreting moderate intakes of sodium chlo-

ride. This state of renal function is analogous to the cardiac reserve with respect to the development of dyspnea in response to the stress of exercise. In a general way, we might classify patients with congestive heart failure according to their tolerance to sodium intake, in analogy with our classification according to the presence of dyspnea with ordinary or less than ordinary activity or at rest. By such a classification patients with mild heart failure might be found capable of taking 4 to 10 Gm. of sodium chloride daily, patients with moderate heart failure might have to be restricted to 2 to 3 Gm. of sodium chloride, whereas many patients with severe heart failure can avoid further sodium retention only by limiting their daily intake to 0.5 to 1.0 Gm. of sodium chloride (or 200 to 400 mg. of sodium).

The degree of sodium restriction must fit the disability in sodium excretion. The routine prescription of 200 mg. of sodium is no more justified for all patients with congestive heart failure than is complete bed rest for patients with exertional dyspnea. On the other hand, the realization that severe heart failure can often be controlled only by this extreme degree of sodium restriction has greatly expanded the value and scope of sodium restriction as a therapeutic measure. Lesser limitations on sodium intake may be tried, but if a satisfactory therapeutic response is not obtained with the aid of other measures, sodium intake must be progressively reduced to 200 mg. or less before the heart failure may be regarded as refractory.

From the viewpoint of treatment, the abnormal retention of sodium is the most important electrolyte disturbance in congestive heart failure. The clinician should not overlook this fundamental fact when an array of other abnormalities in electrolyte patterns compete for conflicting therapeutic attention. Adequate sodium restriction is one of the foundations of the modern effective treatment of congestive heart failure. The physician should offer major resistance to any recommendation that would have him forego this most important therapeutic measure. More particularly he should warily consider any prescription that sodium be administered to a patient with congestive heart failure because of some chemical disturbance in the blood. Whatever merit there may be in hue and cry regarding the possible dangers of "excessive" sodium restriction, one should not overlook the greater danger in all but a few patients with heart failure of omitting or paying lip service to a major therapeutic advance, because of an exaggerated fear of these publicized hazards.

Factors Modifying Electrolyte Patterns in Congestive Heart Failure

Aside from the abnormal retention of sodium, it is uncertain whether there are any distinctive electrolyte disturbances that are specifically related to the heart failure as such. Most of the observed abnormalities in electrolytes can be explained on the basis of complications such as renal impairment, obstructive emphysema, or gastrointestinal disturbances with anorexia, vomiting, or diarrhea, or they may be attributed to therapeutic measures, particularly the use of diuretics in patients on a restricted intake of sodium chloride.

Serum Sodium Concentration in Heart Failure

It is notably difficult to determine the electrolyte pattern in congestive heart failure independent of treatment or complicating diseases. Electrolyte studies are usually made in hospitals where patients arrive only after considerable and often intensive treatment in their homes. Or else they are hospitalized only after the heart failure is advanced and associated with complicating factors.

The basic impairment in sodium excretion in congestive heart failure would lead one to anticipate an elevation of the serum sodium concentration. On the contrary, with few exceptions, most studies have revealed values of serum sodium between 130 and 140 mEq. per L., which may be described as being within a low normal range, or slightly below normal. However, in the study of Iseri and associates,[27] elevated serum sodium values exceeding 150 mEq. per L. were encountered in untreated patients with congestive heart failure. This observation would appear to support the interpretation that the low normal or low values for serum sodium usually reported may be due to a low sodium intake and the use of diuretics in

patients with heart failure, rather than to the heart failure itself. On the other hand, I have noted a tendency to an increased frequency and an increased degree of hyponatremia with increased severity of heart failure, apparently unrelated to therapeutic agents. In severe heart failure low serum sodium values are often observed even when there is no evidence of a significant negative sodium balance. These observations may be interpreted to indicate that increasing hyponatremia represents a parallel consequence or metabolic adjustment to advancing heart failure.

Two important practical therapeutic problems frequently arise in connection with the level of serum sodium in heart failure because many physicians develop a compulsion to correct abnormal chemical findings. First, it must be emphasized that the range of normal serum sodium is much wider than is generally recognized. The commonly stated values of 140 or 143 mEq. per L. must not be interpreted literally. Serum sodium values of 130 to 140 mEq. per L. must be interpreted either as representing normal values or at least as not being responsible for clinical manifestations. Such serum sodium concentrations are not indications for the administration of sodium chloride orally or hypertonic saline intravenously. Second, in the presence of definite hyponatremia, e.g., serum sodium values between 100 and 128 mEq. per L., there is still considerable uncertainty whether the hyponatremia is a consequence of very advanced heart failure and complications, or whether the hyponatremia itself intensifies the heart failure and is responsible for clinical manifestations. If the former is correct, more intensive or improved therapy of heart failure and complications is indicated, not the attempted correction of the blood electrolyte pattern. Exceptions will be indicated below.

Total Body Sodium in Heart Failure

Although the abnormal retention of sodium in congestive heart failure is often associated with a paradoxical reduction in the concentration of serum sodium, the total body sodium in heart failure is considerably elevated, as is anticipated. This increase can be readily calculated from the measurements of the extracellular fluid and the serum concentration of sodium. The latter may be reduced by 5 or 10 per cent, but this reduction is more than compensated by the increase in extracellular fluid by 50 to 100 per cent or more.

More direct measurements have been made of total exchangeable sodium (Na_e) by means of radioactive dilution technics. Warner and co-workers[28] found the mean Na_e in older adult male subjects in congestive heart failure to be 56.7 mEq. per Kg. of body weight (normal, 40 mEq. per Kg.). Aikawa and Fitz,[19] by similar means, found the exchangeable sodium to be increased even more (mean Na 65.3 mEq. per Kg.), presumably due to more severe heart failure in their patients. The exchangeable sodium decreased more than 30 per cent in patients with moderately severe heart failure following intensive therapy. By the use of radioactive sodium to determine exchangeable sodium and antipyrine to measure total body water, a high total sodium to total body water ratio was found in edematous patients with heart disease, signifying that more sodium was retained than water.[20, 29] This disproportionately high retention of sodium relative to water throughout the body, while the concentration of sodium in extracellular water is normal or reduced in heart failure, may indicate that some of the retained sodium finds its way into various tissue cells or into some reservoir such as bone, cartilage, or connective tissue.[29]

Intracellular Sodium in Heart Failure

Calculations of intracellular sodium as well as of other electrolytes have been made indirectly by means of isotope-dilution technics and balance studies in the course of recovery from heart failure as well as by more direct analysis of cardiac and skeletal muscle post mortem[30] and of biopsy specimens of skeletal muscle in vivo.[21, 31] The methods are all unsatisfactory or imperfect and the results have not been consistent. Nevertheless, the studies have generally indicated that intracellular sodium is increased in heart failure. Thus, Mokotoff and associates,[21] in analyses of biopsies of skeletal muscle found the intracellular sodium concentration to be 21.7 mEq. per 100 Gm. of fat-free solids

compared with 11.6 mEq. per 100 Gm. in normal muscle.

Potassium in Heart Failure

The concentration of serum potassium in congestive heart failure is usually normal. Nevertheless there is evidence that the total body stores of potassium are diminished, indicating a loss of intracellular potassium in heart failure. Measurement of the total body potassium by the radioisotope-dilution technic disclosed that total exchangeable potassium (K_e) is diminished in heart failure.[32] During recovery from cardiac failure with edema a positive potassium balance has been reported.[17, 33] This finding suggested that there had been a loss of intracellular potassium during heart failure and that this deficiency was replenished during recovery. Aikawa and Fitz[34] found that the exchangeable potassium (K_e) was depleted during heart failure and replenished when there was a satisfactory therapeutic response, although body weight was decreasing and serum sodium unchanged. An unsatisfactory clinical response and increase in the severity of heart failure or a complication such as pulmonary infarction was accompanied by further decreases in K_e. Direct analysis of skeletal muscle similarly disclosed a reduction in cell potassium according to some observers,[17, 35] although Mokotoff and co-workers[21] found no significant deviation from normal. Iseri and associates[35] found that the potassium concentration of biopsied deltoid muscle was 116 mEq. per L. of intracellular water during frank congestive heart failure and 151 mEq. per L. after restoration of compensation. The loss of cell potassium during the development of heart failure and the accumulation of cardiac edema may be part of a general cellular catabolism, for there is simultaneously a negative nitrogen and phosphorus as well as potassium balance.[36, 37]

The reduction in intracellular and total exchangeable potassium suggested studies to determine the possible value of administering potassium salts to patients with congestive heart failure.[38-40] Laragh[41] observed that when cardiac patients with hyponatremia were given potassium the concentration of serum sodium was restored toward normal. This suggested that the administered potassium entered the cell to replace its deficiency, at the same time releasing sodium to the extracellular fluid. However, no consistent clinical benefit has followed potassium administration except when potassium depletion has been caused by therapeutic agents or complicating factors. It is important to urge caution in the administration of potassium salts to patients with heart failure. There is evidence that such cardiac patients frequently are unable to excrete potassium normally and thus risk the danger of hyperpotassemia. Hyperpotassemia following potassium administration is most likely to occur in the presence of renal impairment, a frequent occurrence in patients with advanced heart failure. In the absence of overt causes for potassium depletion other than heart failure itself, it is doubtful that potassium administration offers any benefit. The potassium depletion appears to be entirely secondary to the heart failure and not responsible for clinical symptoms. Factors that alleviate the heart failure lead to potassium repletion rather than the reverse. Potassium administration is ineffective when the heart failure is inadequately treated or intensified by complications; its administration is unnecessary when heart failure responds to conventional therapy.

Potassium Depletion in Heart Failure

Aside from the diminution in total exchangeable potassium usually associated with uncomplicated heart failure, clinically significant potassium depletion of total body potassium, with or without hypokalemia, may occur as a result of complicating factors or therapeutic agents. Anorexia and nausea are common and may prevent an adequate intake of potassium. Diarrhea or intensive catharsis or enemata may induce active loss of potassium by excessive elimination of intestinal fluids. Overdigitalization may contribute to or be responsible for these gastrointestinal manifestations. The various diuretic agents tend to eliminate potassium, in excess, and when, as is often the case, there is a deficient potassium intake, a negative balance results. Mercurial diuretics eliminate chlorides in combination with sodium and potassium, but especially the latter if the sodium

intake is maximally restricted. Similarly, chloride is excreted in large part with potassium when ammonium chloride is administered as a diuretic or as an adjuvant to the mercurials. Diamox eliminates chiefly bicarbonate among the anions, in combination predominantly with potassium, when dietary sodium is restricted. The cation exchange resins may eliminate potassium in the feces as well as in the urine, the latter by their production of an ammonium chloride acidosis. In the diuretic alkalosis to be described later, potassium depletion may be responsible for some of the symptoms and for renal insufficiency.

Potassium depletion, due to any of the above factors, may be of clinical importance in connection with the problems of digitalis toxicity and intractable heart failure. In the presence of potassium depletion, even proper digitalis dosage will often induce abnormalities in cardiac rhythm and conduction, usually observed only with overdigitalization. Clinical experience has indicated that intractable heart failure is sometimes associated with and presumably due to digitalis intoxication. Responsiveness to therapy appears to be restored as the overdigitalization is corrected by a discontinuation of digitalis medication. But both the arrhythmias associated with digitalis overdosage and the intractable heart failure appear to be corrected more rapidly and more effectively if, in addition to discontinuing digitalis, potassium therapy is instituted.

Diagnosis and Treatment of Potassium Depletion

The administration of potassium salts with the belief that digitalis toxicity and intractable heart failure are causally related, at least in part, to a potassium deficiency, must be undertaken with caution. Sometimes this interpretation is supported by the finding of hypokalemia, but often potassium depletion exists without significant change in the plasma concentration.

When potassium depletion is severe enough to induce clinical manifestations, the following features may be observed: drowsiness, anorexia, nausea, muscular weakness in the extremities varying in severity up to paralysis, diminution or absence of tendon reflexes, weakness or paresis of the muscles of swallowing and respiration, chronic ileus. The diagnosis of potassium deficiency may be indicated or substantiated by the finding of characteristic electrocardiographic abnormalities, e.g., depression of the RS-T segment, prolongation of the Q-T interval, inversion of the T wave, and the presence of a prominent or a biphasic U wave.

Potassium salts should not be administered in the presence of renal insufficiency. If there is doubt as to renal function, but there appears to be a strong indication for potassium salts, they may be administered with careful electrocardiographic control and serial determinations of the plasma potassium concentration. If potassium can be tolerated orally, it may be given in the form of enteric tablets, in a dosage of 1 or 2 Gm. of potassium chloride 3 times daily. A palatable oral preparation containing 10 per cent each of potassium acetate, bicarbonate, and citrate in solution is available commercially as potassium triplex. Each 5 ml. contains approximately 15 mEq. of potassium. One or 2 teaspoonsful of this mixture may be given 3 times daily diluted in fruit juice. If potassium is given intravenously, it may be administered in a solution containing 50 mEq. of potassium (3.7 Gm. of KCl) in 500 or 1000 ml. of 5 per cent glucose in distilled water. The rate of flow should not exceed 20 mEq. of potassium per hour.

Electrolyte Disturbances Associated with Mercurial Diuresis

Repeated mercurial diuresis at short intervals may induce 3 types of response with respect to the blood electrolytes (fig. 1): 1. As a rule, the mercurial diuresis and the subsequent body adjustments in terms of fluid and sodium intake are such that there is no significant disproportion between the loss of sodium and water. Any disproportionate excretion of chloride, relative to sodium, is likewise adjusted. Under these circumstances, the electrolyte pattern is not disturbed despite repeated diuresis. 2. The response regarded as most characteristic following mercurial diuretics is an excretion of chloride in excess of sodium as compared to their relative concentrations in the plasma.[42] The excess chloride is excreted with potassium, ammonium, or both. This may lead to a dis-

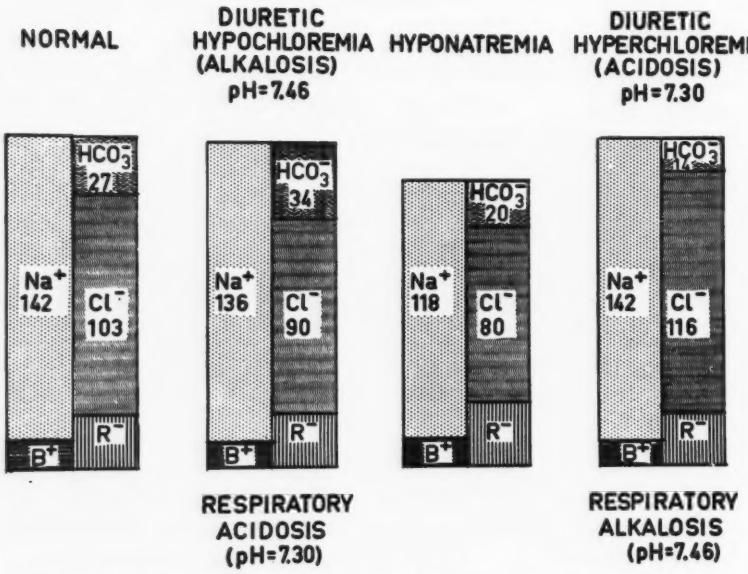

FIG. 1. Electrolyte patterns in congestive heart failure. Gamble-type diagrams. Left-hand columns represent concentrations of chief plasma cations; right-hand columns, the chief plasma anions. Total concentrations equal in each pair, denoting electrochemical neutrality. B^+ denotes positive ions other than sodium, viz., K^+, Ca^{++}, Mg^{++}, etc. R^- denotes negative ions other than chloride and bicarbonate, viz., sulfate, phosphate, protein. From Friedberg, C. K.: Diseases of the Heart. Ed. 2. Philadelphia, W. B. Saunders Co., 1956, p. 276. (Courtesy of the publisher.)

turbance in serum electrolytes that may be termed diuresis hypochloremia. 3. Repeated mercurial diuresis may result in a marked excretion of chlorides, sodium, and water. If water and, to a lesser extent, chlorides are replaced by oral intake of these substances but sodium intake is stringently restricted, a serum electrolyte pattern characterized by hyponatremia may result.

Diuresis Hypochloremia with Alkalosis and Hypokalemia

When mercurial diuretics are repeatedly administered at brief intervals, e.g., daily, there may be a marked reduction in plasma chloride (below 90 mEq. per L.) with little or no reduction in plasma sodium. The excess of serum sodium cations over chloride anions is compensated by an increase in serum bicarbonate with a resultant increase in pH, i.e., alkalosis. At the same time a reduction of plasma potassium may result from the excessive loss of potassium excreted with chloride. In fact it is the excessive excretion of potassium with chloride that induces the alkalosis. The resulting serum electrolyte pattern may be described as hypochloremic alkalosis with hypokalemia.

In some cases of pulmonary disease with severe obstructive emphysema and carbon dioxide retention (respiratory acidosis) there is a similar pattern with regard to the elevation of bicarbonate and the reduction of plasma chloride concentration. But this may be distinguished chemically by the low pH (acidosis) and clinically by the history and findings of obstructive emphysema, as contrasted with the history of profuse and frequent diuresis following mercurial injections in cases of diuresis hypochloremia with alkalosis. Diuresis hypochloremia following the mercurials also resembles the electrolyte pattern observed as a result of vomiting (hydrochloric acid of gastric contents) in cases of pyloric stenosis or other conditions associated with profound or prolonged emesis. The history reveals whether the abnormal electrolyte pattern due to excessive loss of chlorides has been caused by vomiting or mercurial diuresis. Hypochloremia with alkalosis

may result also from conditions in which potassium depletion is the primary event, e.g., diarrhea, intestinal fistula, etc.

Hypochloremic alkalosis in heart failure is likely to follow repeated mercurial diuresis only if simultaneous dietary restrictions or anorexia prevents the replacement of excreted chloride, and especially if there is associated vomiting, e.g., due to digitalis. Conversely, hypochloremic alkalosis following mercurial diuretics may be avoided if ammonium chloride, given prior to or during the mercurial diuresis, provides chloride to replace that lost in the urine. Despite the greater excretory effect of mercurial diuretics on chloride than on sodium ions, hypochloremia results infrequently. Apparently, in most cases, the disproportionate chloride loss is adjusted between diuresis by dietary intake and renal excretion. Therefore several days should usually elapse between mercurial injections, if the diuresis is very profuse. When hypochloremia does occur, it is frequently seen in advanced cases of heart failure in which the renal, adrenal, cellular, or other mechanisms that normally adjust for excessive chloride excretion are not functioning properly. Under such circumstances, with the development of hypochloremic alkalosis, the patient often becomes refractory to diuretics. Failure to respond to mercurial diuretics is an indication for caution in their further administration, for chemical study of the electrolyte pattern, and for critical review of the clinical status and therapy.

The electrolyte disturbance, hypochloremic alkalosis, due to mercurial diuresis, may itself be responsible for unresponsiveness to diuretics. In fact, such unresponsiveness should suggest the possibility of hypochloremia. Since the effect of diuresis due to organomercurials may depend on the specific inhibitory effect of the mercurial diuretic on tubular reabsorption of chloride, this effect may be minimized when plasma chloride falls to low levels and there is a pronounced reduction in the quantity of chloride filtered by the glomeruli. Furthermore, severe hypochloremic alkalosis may itself be responsible for a serious clinical syndrome characterized by refractory heart failure, apathy, anorexia, weakness, somnolence, confusion, and uremia. But there is uncertainty as to whether these and other clinical manifestations are specifically due to the hypochloremic alkalosis or whether the hypochloremia and the clinical manifestations are consequences of the severity of the heart failure, of inadequate or improper therapy, or the presence of complications.

Treatment of Diuresis Hypochloremia with Alkalosis and Hypokalemia

Because of the possibility that the electrolyte disturbance is itself responsible for symptoms and for refractory heart failure, and because clinical improvement and occasionally dramatic improvement have followed correction of the electrolyte pattern, appropriate therapy is indicated. Chloride should be administered cautiously in the form of dilute hydrochloric acid or ammonium chloride. The ammonium ion is metabolized and the free chloride ion has the same effect as that in hydrochloric acid. If the patient can take medication orally, he is given 6 to 9 Gm. of ammonium chloride daily in divided dosage in tablet form. If he is intolerant to this, or if urgent treatment is indicated, ammonium chloride is administered intravenously in a 1 or 2 per cent solution of distilled water containing 5 per cent glucose. Because of the toxicity of the ammonium ion in high concentration (convulsions, shock, coma, and death), ammonium chloride must be given slowly and its rate of administration should not exceed 1 Gm. per hour, nor should more than 10 Gm. be given daily. If there is significant hypokalemia, potassium should also be administered. Sometimes the hypochloremic alkalosis is not corrected until potassium as well as chloride ion is administered. The administered potassium is believed to enter cells as well as the extracellular space. As potassium enters cells, there is an exchange with cellular hydrogen ion, which is transferred to the extracellular fluid, where it reduces the elevated pH and corrects the alkalosis. There is evidence that, when potassium salts are administered to patients with hypochloremic alkalosis, calcium should also be added to avoid tetany.

HYPONATREMIA—THE LOW-SALT SYNDROME

In some patients with severe congestive heart failure, the serum electrolyte pattern is charac-

terized by a striking reduction in the concentration of serum sodium to levels of 130 to 110 mEq. per L. or lower (hyponatremia) (fig. 1). The concentration of serum chloride is likewise diminished but usually to a lesser degree. Consequently the concentration of bicarbonate is also somewhat lowered and there is a mild acidosis. Frequently there is a variable degree of azotemia. Schroeder[43] related a clinical picture to this electrolyte pattern and termed it the "low salt syndrome." This was characterized by hyponatremia, azotemia and refractory heart failure. The syndrome was attributed to the use of mercurial diuretics in patients on a low-sodium intake; renal impairment was regarded as playing an important part in its development. Black and Litchfield[44] reported 8 cases of uremia, 5 of them fatal, among 62 patients with heart failure, presumably due to treatment with low-sodium diets and mercurial diuretics. Many other reports were made of fatalities due to the low salt syndrome or "salt depletion syndrome." The implication of the term low salt syndrome is that depletion of body sodium or the low-plasma-sodium concentration and associated electrolyte disturbances are responsible for a serious clinical picture with progressive cardiac deterioration, uremia, and often with a fatal outcome.

Types of Hyponatremia

It has become increasingly apparent that hyponatremia may result from a variety of mechanisms.[45] Danowski and associates[46] have classified the different types of hyponatremia according to the status of total body stores of sodium: 1. Hyponatremia with diminished total body sodium includes those cases of hyponatremia that are associated with cellular hypo-osmolarity and those that result from excessive depletion of sodium. 2. Hyponatremia with intact total body sodium includes cases of water intoxication and conditions associated with marked hyperlipemia. 3. Hyponatremia with increased total body sodium includes various diseases associated with sodium and water retention such as congestive heart failure, cirrhosis of the liver, and renal disease with the nephrotic syndrome.

Asymptomatic Hyponatremia

A low-sodium concentration in the plasma (below 130 mEq. per L.) is seen in conditions with malnutrition such as chronic tuberculosis,[47] without any clinical manifestations of the so-called low-sodium syndrome and in fact without any symptoms that can be attributed to the hyponatremia. This indicates that hyponatremia per se is not necessarily responsible for clinical features. The hypo-osmolarity in this chronic asymptomatic form of hyponatremia may be due to nutritional disturbances effecting primarily cellular electrolyte concentration. The low plasma (and extracellular) sodium concentration may represent a secondary adjustment whereby sodium metabolism is regulated around this new low homeostatic level. Although these cases should be distinguished from those with heart failure and hyponatremia, it is possible that malnutrition may be partly responsible for hyponatremia in some of the cases of heart failure.

Depletion Hyponatremia

Among the various cases of hyponatremia occurring in congestive heart failure, the hyponatremia in one group may be truly attributed to sodium depletion. In the latter group drastic diuretic therapy with profuse diuresis and natriuresis, combined with a low-sodium intake, may result in a markedly negative sodium balance and a reduction in both total body sodium and serum sodium concentration. Repeated thoracentesis with removal of large quantities of pleural fluid or repeated paracentesis of large quantities of ascitic fluid are particularly likely to induce sodium depletion and hyponatremia.[48] Diarrhea or extreme sweating in hot climates or in hot weather may contribute to sodium depletion induced by mercurial diuretics. In such patients the onset of clinical and chemical features of sodium depletion may appear rather acutely after the diuresis or after the pleural or abdominal tap. In this type of hyponatremia due to sodium depletion, dilution of electrolytes, due to greater loss of sodium than water, may account in part for the lowered serum sodium, but external loss of sodium is the primary factor. Furthermore, the total quantity of body sodium is diminished.

Dilution Hyponatremia

In the majority of cases of hyponatremia associated with heart failure, sodium depletion is not the responsible mechanism, as has been commonly assumed. A minimal intake of sodium is contributory, but there is no evidence of abnormal sodium loss externally. Total body sodium is considerably increased. Whatever the role of the mercurial diuretics, they do not act by causing a profuse diuresis of sodium and consequent sodium depletion. The concentration of sodium in the urine is extremely low or virtually absent even after the administration of a mercurial diuretic. While the sodium intake is extremely low, the fluid intake is usually unrestricted and there may be a positive water balance in view of the common oliguria. Thus the hyponatremia results from water dilution of the extracellular sodium. This type of dilution hyponatremia in heart failure may be complicated by sodium depletion when there are repeated thoracenteses, abdominal paracenteses, or gastrointestinal disturbances with diarrhea.

The explanation for this disproportionate retention of water when sodium intake and excretion are minimal is not clear. Associated renal impairment may be an important if not an essential underlying factor. The low-sodium intake and the mercurial diuretics may be concerned in producing or intensifying the renal impairment that leads to water retention and sodium dilution. Although water excretion by the kidney in heart failure is generally regarded as normal except insofar as water is retained secondary to sodium, there is evidence that, especially in advanced stages of heart failure, a water load is poorly excreted.[49] Liberal intakes of fluid result in a positive water balance and sodium dilution when the sodium intake is restricted.

The impairment of water diuresis may be due to increased secretion of the antidiuretic hormone (ADH) in advanced heart failure[50] rather than to renal impairment, as suggested by the similarity of the clinical picture induced by the administration of pitressin tannate in oil to patients with heart failure on a liberal water and very low sodium intake. Perhaps the most important factor in accounting for dilution hyponatremia is the state of the circulation, i.e., the advanced stage of congestive heart failure. Intractable heart failure is a characteristic feature of dilution hyponatremia. Frequently the intractability of the heart failure is attributed to the abnormality in the electrolyte pattern. But efforts to correct the hyponatremia by the administration of hypertonic sodium chloride do not usually improve and may intensify the heart failure, even when the serum sodium concentration is increased toward normal. It appears probable that the occurrence of dilution hyponatremia is itself a manifestation of advanced or intractable heart failure rather than a cause of it. However, extreme restriction of sodium coupled with the administration of mercurial diuretics may further impair the renal excretion of water as well as of sodium at this stage of heart failure, instead of inducing diuresis and clinical improvement, as they do when heart failure is less severe and still responsive to therapy.

Ordinarily, homeostatic mechanisms tend to restore both the normal osmotic tension and the volume of the extracellular fluid. A diminution in osmotic tension (as indicated by diminished plasma sodium concentration) is compensated by inhibition of ADH secretion and increased excretion of water, and an increased extracellular volume is compensated by an increased excretion of sodium and water.[51] With progressive heart failure the homeostatic levels appear to be revised to higher levels of extracellular volume and lower levels of osmotic tension. It seems as if progressive cardiac failure produces increasingly powerful stimuli that induce both sodium and water retention, and that overcome the normal stimuli and regulatory mechanisms that would otherwise tend to increase sodium and water excretion when the extracellular volume is increased, and increase water excretion when the extracellular fluid is hypotonic.[1, 52] What these abnormal stimuli are, and how they are initiated and mediated, is largely speculative. One may speculate also whether revision of the extracellular osmostat to a lower level of sodium concentration may be of benefit in heart failure, since there is some evidence that impaired myocardial contraction of the isolated heart may be restored by reduc-

ing the sodium concentration in the perfusing fluid.

Whether the dilution of serum leading to hyponatremia is entirely explained by the continued unrestricted intake of water at the same time that sodium intake is restricted, or whether it is due to a disproportionate retention of water relative to sodium or to intracellular-extracellular shifts of sodium and water is uncertain.[53] In heart failure total body sodium is increased to a greater extent than total body water, even in cases with hyponatremia. Thus the hyponatremia cannot be explained by simple dilution due to retention of water in excess of sodium. Water retention results in dilution of sodium in the extracellular space, i.e., in hyponatremia, because there must be a shift of sodium out of the extracellular space into cells or a storage in other tissue such as bone and tendon.

Clinical Features of Hyponatremia

The clinical features depend on the type of hyponatremia. The hyponatremia sometimes associated with tuberculosis and other chronic wasting diseases is asymptomatic. The hyponatremia due to sodium depletion is associated with a distinctive clinical picture that is characterized by a relatively acute onset, circulatory insufficiency (shock), renal insufficiency, and multiple other symptoms, especially weakness, muscle cramps, apathy, anorexia, and somnolence. The clinical picture associated with the dilution type of hyponatremia develops more insidiously and is less likely to be associated with circulatory collapse (shock) or with muscle cramps. Anorexia and apathy are early symptoms. Nausea and vomiting occur and the patient is drowsy most of the day. There is a poor diuretic response to mercurial diuretics. Oliguria and azotemia become progressively more severe and edema persists or increases, despite an extremely low sodium intake and the administration of diuretics. Uremia and mental symptoms become more prominent. Restlessness, confusion, convulsions and coma may occur, and there is usually a fatal outcome. Although the serum electrolyte pattern in depletion and in dilution hyponatremia is essentially identical, the two conditions may be distinguished by a careful history of the sequence of development and exact nature of the symptoms and by the evidence of actual external sodium losses in the depletion type (profuse diureses, paracenteses, thoracenteses) but not in the dilution type of hyponatremia.

Many of the features attributed to the low-sodium syndrome are nonspecific and could be due to other disturbances or complications frequently observed in congestive heart failure. Concomitant pulmonary embolism, digitalis intoxication, intrinsic renal disease with renal insufficiency, acute myocardial infarction, internal bleeding from anticoagulants, intercurrent infection, and intractable and irreversible heart failure are among the conditions that produce the clinical picture often attributed to hyponatremia.

Treatment of Hyponatremia

When hyponatremia is due to sodium depletion, treatment consists in increasing sodium intake by mouth in mild cases. Hypertonic sodium chloride (300 ml. of a 3 per cent or 5 per cent solution) is administered intravenously when the need is more urgent or the patient is unable to take sodium orally. In the presence of significant acidosis a 5 per cent sodium bicarbonate of 1/6 molar sodium lactate solution should be administered intravenously. Too vigorous efforts to raise the sodium concentration to normal involve the risk of increasing anasarca and acute pulmonary edema.

When hyponatremia is of the dilution type, one should consider carefully other possible causes of the clinical picture than hyponatremia. Overdigitalization should be corrected. A careful survey is made of all possible complicating factors or of imperfections in therapy that may account for the intractable heart failure that is often the reason for the hyponatremia. If such complications and therapeutic imperfections can be found and corrected, the heart failure may be alleviated and the hyponatremia simultaneously corrected without direct attempts to correct the chemical changes.

Fluids as well as sodium should be restricted in cases of dilution hyponatremia with oliguria almost as stringently as in cases of acute oli-

guria due to toxic nephrosis (lower nephron nephrosis). The fluid intake should not exceed the urinary output plus 500 ml. to allow for fluid loss by insensible perspiration. The administration of sodium orally or intravenously in patients with dilution hyponatremia is contraindicated, even though such measures have sometimes been carried out without apparent harm. Although the concentration of serum sodium can be elevated and the abnormal electrolyte pattern deviated toward normal, clinical improvement is rare, is usually due to other factors, and the fatal outcome is rarely altered. The reported rise in serum sodium following the administration of potassium chloride has rarely been accompanied by a significant diuresis or clinical improvement. Attention is again directed to the necessary caution in administering potassium to patients in heart failure.

Hyperchloremic Acidosis

This abnormal blood electrolyte pattern is characterized by an elevated serum chloride concentration (above 110 mEq. per L.), by a reduction in bicarbonate concentration (below 20 mM per L.), and by a reduction in the pH of the serum (fig. 1). Serum sodium concentration is usually normal. Azotemia may be associated. In cases of heart failure this abnormal serum electrolyte pattern is due to the prolonged administration of large doses of ammonium chloride. However, serious acidosis is most likely to occur in the presence of renal insufficiency. Less severe degrees of hyperchloremic acidosis may be caused by cationic resin therapy or by the carbonic anhydrase inhibitor, acetazolamide (Diamox). Sometimes severe hyperchloremic acidosis is due to combinations of these agents.

When ammonium chloride is administered, the ammonium ion is metabolized by the liver. The remaining hydrochloric acid reduces serum bicarbonate. Increased pulmonary ventilation, by eliminating more carbon dioxide, tends to cause a compensatory reduction in serum carbon dioxide. In the kidney, the excess chloride tends to be eliminated in combination with sodium and potassium, but these cations are partially conserved by the aid of buffer salts and by ammonia produced by the kidney. When sodium intake is low, chloride is eliminated chiefly in combination with potassium. Cationic resins have a similar effect by combining with cations and releasing ammonium chloride or hydrochloric acid, which are absorbed from the gastrointestinal tract. Diamox inhibits carbonic anhydrase and the secretion of hydrogen ions by the renal tubules, thereby inhibiting the dissociation of bicarbonate in the tubules and causing large quantities of bicarbonate to be excreted with sodium and potassium. This results in a reduced serum bicarbonate, increased chloride, and acidosis.

An increasing number of cases with serious clinical manifestations of ammonium chloride acidosis are being observed.[54-56] The clinical picture consists of anorexia, nausea, vomiting, restlessness, confusion, lassitude, or somnolence progressing to pronounced stupor and areflexia. Hyperventilation and Kussmaul type of respiration has many times, in my experience, been mistaken for the dyspnea of intractable heart failure. In other cases in which hyperpnea, coma, and azotemia are the outstanding findings, the clinical picture has been misinterpreted as being due to diabetic acidosis, intrinsic renal insufficiency, or a cerebrovascular accident.

The treatment of ammonium chloride acidosis is primarily the discontinuation of ammonium chloride administration. But when severe clinical symptoms are present, especially stupor or coma, an isotonic solution of 5 per cent sodium bicarbonate of 1/6 molar lactic acid should be administered intravenously. Two or 3 L. of these solutions may have to be given over a period of 12 to 24 hours. The risk of increasing edema or of pulmonary edema may be minimized by raising the head of the bed, as well as the head and shoulders of the patient, by administering the solution slowly, and especially by continuous clinical observation and repeated chemical studies of the blood. The intravenous administration of sodium glutamate has been reported to reduce blood ammonia and to ameliorate the symptoms of ammonia intoxication, especially when due to ammonium chloride administration. On the other hand, the results in hepatic coma have been discouraging.[57] Twenty-nine grams of so-

dium glutamate in 1000 ml. of 5 per cent glucose in distilled water is administered by slow intravenous drip over a period of 4 hours.

Severe ammonium chloride acidosis should be prevented if there is a clear understanding of the action of ammonium chloride and of its limitations as well as usefulness. It is eliminated chiefly with potassium when sodium intake is restricted. After a few days it is eliminated also with ammonium ion produced by the kidney. Its chief purpose is to prevent or restore chloride deficits caused by mercurial diuresis, and thereby is useful as an adjunct to mercurial diuretic therapy, especially when the latter becomes less effective because of chloride depletion. For this purpose ammonium chloride should be given intermittently for 2 or 3 days at a time; standing orders for ammonium chloride and prolonged continuous administration are hazardous. The drug is contraindicated in the presence of renal insufficiency due to intrinsic renal disease, but not when azotemia is due to hypochloremic alkalosis caused by mercurial diuresis. Recently, controlled hyperchloremic acidosis induced by the combined administration of ammonium chloride and Diamox has been found useful in restoring the effectiveness of mercurial diuretics in cases of refractory heart failure that have become "mercury fast."[58] This technic may be an extremely valuable one that can be utilized with minimal hazard only if the induction of acidosis is controlled by careful clinical observation and chemical studies of the blood. Administration of ammonium chloride may be hazardous in the presence of hepatic insufficiency if the liver cannot metabolize the toxic ammonium ion. This risk must be considered in cases of advanced right heart failure with functional tricuspid insufficiency and cardiac cirrhosis.[59]

Effects of Pulmonary (Respiratory) and Renal Insufficiency

Maintenance of the normal electrolyte pattern and especially of the acid-base balance is controlled largely by the kidneys and to a lesser extent by pulmonary function. Congestive heart failure is frequently associated with or complicated by renal insufficiency and occasionally by pulmonary emphysema with respiratory insufficiency. Electrolyte disturbances due to heart failure itself or to therapeutic measures for heart failure may be modified or exaggerated by renal or respiratory insufficiency.

Renal impairment, which is common with advanced heart failure, may be due to or intensified by the frequent administration of mercurial diuretics in patients on very low sodium diets. Severe renal insufficiency is accompanied by a retention of organic acids, phosphates, and sulfates that results in acidosis and a reduction in both serum bicarbonate and chlorides, whereas the concentration of serum sodium is reduced to a variable but lesser degree.

The hyperventilation associated with left heart failure increases the pulmonary elimination of carbon dioxide and may cause a slight reduction in serum carbon dioxide and bicarbonate (respiratory alkalosis). In the presence of severe complicating emphysema or when the emphysema is itself the cause of heart failure (cor pulmonale), carbon dioxide cannot be eliminated normally and excessive carbon dioxide is retained in the serum. The increased serum content of carbon dioxide (hypercapnia) is associated with a compensatory increase in serum bicarbonate and reduction in serum chloride. The hypochloremia with increased bicarbonate is, however, accompanied by a reduction in serum pH, since the elevation in bicarbonate does not quite compensate for the increased carbon dioxide. In this respect the pattern differs from the hypochloremia with high bicarbonate sometimes observed following mercurial diuresis, since the pH is elevated in the latter, i.e., there is alkalosis instead of acidosis. Clinical evaluation or determination of the serum pH differentiates these from electrolyte patterns. The clinical history and findings should always be considered in trying to determine the mechanism responsible for electrolyte disturbances in heart failure, and especially when attempting to correct the electrolyte disturbance. It would hardly be laudable, however enthusiastic, if ammonium chloride were prescribed in the patient with heart failure and hypochloremia on the assumption that the latter was due to mercurial diuresis, when it

was actually due to renal insufficiency and acidosis or to obstructive emphysema with carbon dioxide retention (respiratory acidosis).

Relation of Chloride and Sodium Ions

When, prior to the availability of the flame photometer, sodium determinations were difficult to perform, chlorides were measured and used as a gage of sodium concentration and sodium metabolism. This procedure, however, often leads to erroneous interpretations, since there may be a significant dissociation between chloride and sodium behavior. Although low-sodium diets usually mean low-sodium chloride and therefore low-chloride diets, sodium intake may be reduced to a minimum while chloride is being ingested in combination with other cations than sodium. Thus the patient may be taking salt substitutes containing potassium chloride or ammonium chloride as an adjuvant to diuresis. Urinary chloride measurements may show relatively high values and be misleading if the chloride values are used to estimate urinary sodium output, either to check on the dietary intake of sodium or the effect of diuretics. In the hypochloremic alkalosis due to mercurial diuretics serum sodium is usually normal while chlorides are diminished, since these diuretics induce a greater chloride than sodium excretion in comparison with their serum concentrations. Likewise, in respiratory acidosis with carbon dioxide retention due to obstructive pulmonary emphysema, the serum sodium concentration is usually normal while chloride is lowered.

Relation of Electrolyte Disturbances to Mechanism of Heart Failure

The possible relationship of electrolyte disturbances to the mechanism of heart failure has engendered extensive discussion in recent years. Insofar as heart failure represents failure of the heart as a muscular pump to maintain an adequate output or to expel a normal input, we will consider the possible role of electrolytes in maintaining normal cardiac contraction. Insofar as heart failure represents a clinical syndrome determined by an abnormal volume and distribution of extracellular fluid, we will discuss the mechanisms by which heart failure results in such abnormalities.

Electrolytes and Cardiac Contraction

That electrolytes are essential for, and may modify, cardiac contraction is well known. The isolated heart, when perfused by 0.6 per cent sodium chloride solution, soon stops in diastole. The addition of potassium solution antagonizes the sodium effect and restores cardiac contraction. Calcium, in the absence of potassium, increases the duration of systole at the expense of diastole and eventually produces calcium rigor. Potassium, in excess, prolongs diastole and may cause inhibition and arrest of the heart. It is now known that normal cardiac contraction requires potassium, calcium, and sodium, among other electrolytes, in appropriate concentration.

Recent knowledge of the chemical factors underlying the contraction of skeletal muscle has been applied also to the contraction of the heart. The electrolytes, potassium, sodium, magnesium, calcium, and perhaps other ions, are important in the regulation of the reactions involved in myocardial contraction. According to a dominant theory, the muscle proteins, actin and myosin, prior to contraction, are dissociated from each other, in the presence of a normal concentration of potassium ions. The excitatory impulse initiated at the sinoatrial node depolarizes the cell membrane and causes it to become more permeable to ions, notably, potassium. There is an egress of potassium ions with a reduction in the potassium gradient. The reduction in muscle cell potassium concentration permits the union of actin and myosin to form long molecules of viscous strands of actomyosin. The presence and concentration of potassium and other ions may also be important in regulating the adsorption of adenosine triphosphate onto myosin and the subsequent contraction of the actomyosin-adenosine triphosphate complex.

Considerable experimental evidence indicates that the tension developed by a muscle fiber is closely related to changes in its potassium content.[60] A relationship to sodium is indicated by the observation that isolated, resting rat's cardiac muscle in Krebs solution takes up sodium

and loses potassium.[61] Stimulation of the muscle decreases intracellular potassium with probable sodium uptake. The contractile response is impaired and sodium uptake is increased in the presence of anoxia. With restored oxygenation of the myocardium the contractile response is improved but complete recovery occurs if the sodium concentration of the bath solution is reduced.[62] Both in the isolated rat's ventricle and the glycerol-extracted myocardial fiber, contractile strength is promoted by diminishing the sodium concentration in the perfusion solution and contractile strength is impaired when the sodium concentration is augmented.[63]

At the present time there appears to be no disturbance in the generation of energy by the myocardium in most forms of congestive heart failure, but rather a deficiency in the conversion of this energy to useful work. Although normal electrolyte concentrations are essential to proper cardiac contraction, there is no evidence that electrolyte disturbances are important in the initial failure of the heart as a muscular pump. It is probable, however, that when serious electrolyte disturbances develop after heart failure is established, these disturbances may further impair myocardial contraction.

The beneficial action of digitalis in heart failure is pertinent to this discussion because of the relations of digitalis to electrolytes. It has been observed that digitalis may cause toxic cardiac arrhythmias that may be prevented or eliminated by potassium salts and that occur more readily with potassium depletion. The isometric tension of the isolated papillary muscle is enhanced by a diminished extracellular potassium or increased calcium concentration and lowered by an increase in extracellular potassium. The administration of therapeutic doses of digitalis causes an egress of potassium from heart muscle, as determined by analysis of simultaneous samples of blood from the brachial artery and catheterized coronary sinus in patients with low-output heart failure.[64] This egress is associated with changes in transmembrane potentials and marked acceleration of repolarization. At present the beneficial action of digitalis is usually ascribed to improved utilization of phosphate-bone energy by actomyosin fibers but this may be effected in part by the action of digitalis on potassium and other electrolyte exchanges and on transmembrane potentials.

Electrolytes and the Clinical Picture of Heart Failure

In contrast with the questionable role of electrolyte disturbances in failure of the heart as a pump, electrolyte disturbances are of fundamental importance in the production of the clinical picture of heart failure. We have discussed the generally accepted finding of abnormal sodium retention of water, which is responsible for many of the clinical features. Emphasis on the diminished cardiac output, disproportionate reduction in renal blood flow, diminished glomerular filtration, and increased renal tubular reabsorption of sodium has led to the so-called forward-failure theory of heart failure. The backward-failure theory laid greater emphasis on the increased congestion and increased venocapillary pressure behind the failing chambers of the heart as the primary factors in the production of edema and related symptoms of heart failure.

Conflict regarding advocacy of the one or the other theory has been largely dissipated in recent years. In a continuous circulation it is impossible to have "forward" failure without "backward" failure or vice versa. The important role of increased venocapillary congestion and elevated venocapillary pressure in inducing clinical symptoms, including edema by transudation of plasma water, cannot be denied. Furthermore, the organ site of symptoms and the localization of increased extracellular fluid are determined by these hemodynamic changes. On the other hand, it is apparent that without sodium and water retention by the kidney, the increased extracellular fluid cannot be explained by increased capillary pressure and transudation of plasma water, since the increased extracellular fluid far exceeds the total amount of plasma.

At present there is speculative discussion regarding the manner in which the occurrence of heart failure initiates and controls renal retention of sodium and water. Obstruction and elevation of pressure in the renal vein, in the

inferior vena cava,[65] in the superior vena cava[65] and compression of the neck[66] may initiate renal sodium retention. These and related observations have given rise to the hypothesis that there is a volume regulator that controls extracellular volume by means of renal excretion of sodium and water and that the stimulus on the afferent side is either the cardiac output, venous return, effective blood volume, or the pressure in critical venous segments. Although there are many gaps in the hypothesis, it has been postulated that the volume regulator is set at a new abnormal level in heart failure, whereby sodium and water are retained, although other homeostatic mechanisms would tend to excrete water when the extracellular fluid is increased and when the extracellular osmotic pressure is diminished.

The renal retention of sodium and water may be mediated in part by increased aldosterone secretion and antidiuretic hormone, but the clinical picture of heart failure is not a simple consequence of hyperaldosteronism or an excess of pituitary antidiuretic hormone. Aldosterone secretion is normally concerned with renal conservation of sodium and the latter is abnormally exaggerated in heart failure.[67] Although only small amounts of aldosterone are normally detectable in the urine, in heart failure and other edematous states excessive quantities of aldosterone are excreted.[68] To some extent the increased aldosterone secretion may be due to sodium deprivation, since patients in heart failure have a sodium-restricted diet.[69] Despite the correlation of aldosterone excretion with heart failure, the former is not a primary event, for in socalled primary aldosteronism the clinical picture differs notably from heart failure, especially in the absence of edema.[70]

The relation of pituitary antidiuretic hormone to the water retention in heart failure is even more uncertain. The repeated intramuscular administration of pitressin tannate to cardiac patients results in marked water retention and a clinical picture resembling intractable heart failure.[71] But available evidence indicates that there is no increased sensitivity and no impaired metabolism of ADH in heart failure.[50, 72] In the absence of significant renal disease the water retention in heart failure appears to be secondary to sodium retention. In advanced heart failure there may be excessive production of ADH due to some unknown stimulus independent of osmoreceptors and even with diminished osmolarity of the plasma.[50] Other observations indicate that there is no relation between the retention of water and increased plasma ADH in heart failure.[73]

Conclusion

Heart failure is associated with a variety of electrolyte disturbances, some of them attributed to the effects of intensive or excessive use of therapeutic agents or to gastrointestinal, renal, or pulmonary disturbances associated with heart failure. These electrolyte disturbances may themselves be responsible for serious clinical symptoms and they may also render the heart failure intractable and unresponsive to therapeutic agents, particularly the mercurial diuretics. Consequently there has been great emphasis in recent years on the avoidance of these electrolyte disturbances and especially on their recognition and correction when they occur.

On the other hand, it has been stressed that the fundamental electrolyte disturbance in heart failure is the abnormal retention of sodium and that the dramatic improvement in the outlook of patients with heart failure in recent years has been due to correction of this abnormality by a more effective use of very low sodium diets and mercurial diuretics. The current emphasis on the hazards of electrolyte disturbances in heart failure due to therapeutic agents has been so intense that many physicians have become excessively cautious in their use of low-sodium diets and mercurial diuretics, thus foregoing a major therapeutic advance in the management of heart failure. Considering the number of patients with heart failure and the usually long life history of heart failure, serious electrolyte disturbances are relatively infrequent and usually occur only in advanced stages of the disease. With proper understanding of blood electrolyte patterns in heart failure and with reasonable caution, it is possible to avoid serious electrolyte disturbances without

surrendering the advantages of sodium restriction and mercurial diuresis, fully utilized for maximum therapeutic effect. When a patient with heart failure becomes refractory to treatment, an electrolyte disturbance must be considered as one among many possible causes. But hypertonic sodium chloride should not be hastily administered unless all of the more frequent causes of intractable heart failure have been carefully excluded and the presence of sodium depletion has been definitely established by the clinical history and detailed study of the blood electrolyte pattern. It is becoming increasingly apparent that the unfavorable clinical picture associated with electrolyte disturbances is usually not due to these electrolyte disturbances. Rather the clinical picture and the electrolyte aberrations are both consequences of the inexorable progression of the serious underlying cardiac disease and its complications. As a rule, a careful reappraisal and improvement in therapy and the elimination of complications are more likely to correct both the heart failure and the electrolyte disturbances than the intravenous administration of electrolytes designed to correct a chemical abnormality.

However, electrolyte disturbances have usually been of primary responsibility for the clinical picture under the following circumstances: repeated removal of pleural or ascitic fluid or profuse mercurial diuresis, especially in hot weather, may lead to true sodium depletion, with hyponatremia, muscular cramps, and a shock-like state. In such cases cautious sodium replacement is necessary and beneficial. This does not apply to the much more common form of dilution hyponatremia in which neither muscle cramps nor shock occurs, and in which there is no satisfactory diuresis or other cause for sodium depletion. Electrolyte disturbances are clinically significant also in the cases of ammonium chloride acidosis. These can usually be avoided by using ammonium chloride only intermittently, in moderate dosage, and not in the presence of renal or hepatic insufficiency. This clinical state is readily controlled if its nature is recognized early. Hypochloremic alkalosis may be avoided if mercurial diuretics are given as required and not with unnecessary frequency. Furthermore, ammonium chloride should be supplied intermittently whenever mercurial diuretics are given frequently and are followed by a profuse diuresis. Potassium depletion is perhaps the commonest electrolyte disturbance in heart failure that is being frequently overlooked. It may not be reflected in serum potassium determinations. Whenever anorexia and nausea prevent an adequate intake of potassium and especially when there is associated diarrhea, which is often overlooked in practice, potassium depletion is likely to be present, especially since both the heart failure itself and many of the drugs used contribute to potassium depletion. This depletion can be avoided only by a constant check on the adequacy of potassium intake in the diet, and by more than casual query as to bowel function.

REFERENCES*

[1] FRIEDBERG, C. K.: Electrolyte and fluid disturbances in congestive heart failure. New England J. Med. **245:** 852, 1951.

[2] PRENTICE, T. C., SIRI, W., BERLIN, N. I., HYDE, G. M., PARSONS, R. J., JOINER, E. E., AND LAWRENCE, J. H.: Studies of total body water with tritium. J. Clin. Invest. **31:** 412, 1952.

[3] IKKOS, D.: Comparison of the volume of distribution of sucrose, inulin and thiosulfate in human subjects. Metabolism **4:** 19, 1955.

[4] FREINKEL, N., SCHREINER, G. E., AND ATHENS, J. W.: Simultaneous distribution of T-1824 and I^{131}-labelled human serum albumin in man. J. Clin. Invest. **32:** 138, 1953.

[5] FRANK, H., AND GRAY, S. J.: The determination of plasma volume in man with radioactive chromic chloride. J. Clin. Invest. **32:** 991, 1953.

[6] FORBES, G. B., AND PERLEY, A.: Estimation of total body sodium by isotopic dilution. I. Studies in young adults. J. Clin. Invest. **30:** 558, 1951.

[7] — AND LEWIS, A.: Relation of exchangeable sodium, potassium and chloride to total body content in man. J. Clin. Invest. **35:** 703, 1956.

[8] — AND —: Total sodium, potassium and chloride in adult man. J. Clin. Invest. **35:** 596, 1956.

[9] EDELMAN, I. S., JAMES, A. H., BADEN, H., AND MOORE, F. D.: Electrolyte composition of bone and the penetration of radiosodium and deuterium oxide into dog and human bone. J. Clin. Invest. **32:** 122, 1954.

[10] BERGSTROM, W. H., AND WALLACE, W. M.: Bone as a sodium and potassium reservoir. J. Clin. Invest. **33:** 867, 1954.

* For additional references prior to 1951, see reference no. 1.

[11] Deane, N., and Smith, H. W.: The distribution of sodium and potassium in man. J. Clin. Invest. **31:** 197, 1952.

[12] Conway, E. J.: The biological performance of osmotic work. A Redox pump. Science **113:** 270, 1951.

[13] Osterhout, W. J. V.: The mechanism of accumulation in living cells. J. Gen. Physiol. **35:** 579, 1952.

[14] Thomas, C. A., Jr.: New scheme for performance of osmotic work by membranes. Science **123:** 60, 1956.

[15] Hurst, W. W.: Simultaneous determination of body water by deuterium and antipyrine in patients with edema. Am. J. Med. **10:** 516, 1951.

[16] Miller, G. E.: Water and electrolyte metabolism in congestive heart failure. Circulation **4:** 270, 1951.

[17] Squires, R. D., Crosley, A. P., and Elkinton, J. R.: The distribution of body fluids on congestive heart failure. III. Exchanges in patients during diuresis. Circulation **4:** 868, 1951.

[18] Lusk, J. A., III, and Palmer, S. D.: Sodium exchange in congestive heart failure. Circulation **8:** 282, 1953.

[19] Aikawa, J. K., and Fitz, R. H.: Alterations in exchangeable sodium content, "sodium^{24} space" and body weight during the treatment of congestive failure. Circulation **12:** 897, 1955.

[20] Farber, S. J., and Soberman, R. J.: Total body water and total exchangeable sodium in edematous states due to cardiac, renal or hepatic disease. J. Clin. Invest. **35:** 779, 1956.

[21] Mokotoff, R., Ross, G., and Leiter, L.: The electrolyte content of skeletal muscle in congestive heart failure; a comparison of results with inulin and chloride as reference standards for extracellular water. J. Clin. Invest. **31:** 291, 1952.

[22] Schwartz, I. L., Schachter, D., and Freinkel, N.: Measurement of extracellular fluid in man by means of a constant infusion technique. J. Clin. Invest. **28:** 1117, 1949.

[23] Walser, M., Duffy, B. J., Jr., and Griffith, H. W.: Body fluids in hypertension and mild heart failure. J.A.M.A. **160:** 858, 1956.

[24] Schreiber, S. S., Bauman, A., Yalow, R. S., and Berson, S. A.: Blood volume alteration in congestive heart failure. J. Clin. Invest. **33:** 578, 1954.

[25] Gunton, R. W., and Paul, W.: Blood volume in congestive heart failure. J. Clin. Invest. **34:** 879, 1955.

[26] Friedberg, C. K.: Diseases of the Heart. Ed. 2. Philadelphia, W. B. Saunders Co., 1956, p. 170.

[27] Iseri, L. T., McCaughey, R. S., Boyle, A. J., and Myers, G. B.: Plasma sodium and potassium concentrations in congestive heart failure. Am. J. M. Sc. **224:** 135, 1952.

[28] Warner, G. F., Dobson, E. L., Rodger, C. E., Johnston, M. E., and Pace, N.: The measurement of total "sodium space" and total body sodium in normal individuals and in patients with cardiac edema. Circulation **5:** 915, 1952.

[29] Talso, P. J., Spafford, N., Ferenzi, G., and Jackson, H. O.: Paradoxical hyponatremia associated with congestive heart failure and with cirrhosis of the liver. Metabolism **5:** 58, 1956.

[30] Clarke, N. E., and Mosher, R. E.: The water and electrolyte content of the human heart in congestive heart failure with and without digitalization. Circulation **5:** 907, 1952.

[31] Talso, P. J., Spafford, N., and Blaw, M.: The metabolism of water and electrolytes in congestive heart failure. II. The distribution of water and electrolytes in skeletal muscle in edematous patients with congestive failure before and after treatment. J. Lab. & Clin. Med. **41:** 405, 1953.

[32] Burrows, B. A., Ashley, M. M., and Sisson, J. H.: Radioactive potassium distribution in metabolic disorders. Abstracted, J. Clin. Invest. **31:** 620, 1952.

[33] Mader, I. J., Morita, Y., and Iseri, L. T.: Sodium, potassium and magnesium balance during recovery from congestive heart failure due to cor pulmonale and other heart diseases. Circulation **12:** 1057, 1955.

[34] Aikawa, J. K., and Fitz, R. H.: Alterations in exchangeable potassium content during the therapy of congestive failure. Clin. Res. Proc. **4:** 106, 1956.

[35] Iseri, L. T., Boyle, A. J., Chandler, D. E., and Myers, G. B.: Electrolyte studies in heart failure. I. Cellular features in the pathogenesis of the edema of congestive heart failure. Circulation **11:** 615, 1955.

[36] Sinclair-Smith, B., Kattus, A. A., Genest, J., and Neuman, E. V.: The renal mechanism of electrolyte excretion and the metabolic balances of electrolytes and nitrogen in congestive cardiac failure: The effects of exercise, rest and aminophylline. Bull. Johns Hopkins Hosp. **84:** 369, 1949.

[37] Iseri, L. T., Boyle, A. J., and Myers, G. B.: Water and electrolyte balance during recovery from severe congestive failure on a 50 mg. sodium diet. Am. Heart J. **40:** 706, 1950.

[38] Fox, C. L., Friedberg, C. K., and White, A. G.: Electrolyte abnormalities in chronic congestive heart failure; effects of administration of potassium and sodium salts. Abstracted, J. Clin. Invest. **28:** 781, 1949.

[39] Elkinton, J. R., Squires, R. D., and Bluemle, L. W.: The distribution of body fluid in congestive heart failure. Circulation **5:** 58, 1952.

[40] Cort, J. H., and Matthews, H. L.: Potassium deficiency in congestive heart failure. Three cases with hyponatremia including results of

potassium replacement in one case. Lancet **1:** 1202, 1954.

[41] LARAGH, J. H.: The effect of potassium chloride on hyponatremia. J. Clin. Invest. **33:** 807, 1954.

[42] SCHWARTZ, W. B., AND WALLACE, W. M.: Electrolyte equilibrium during mercurial diuresis. J. Clin. Invest. **30:** 1089, 1951.

[43] SCHROEDER, H. A.: Renal failure associated with low extracellular sodium chloride. Low salt syndrome. J.A.M.A. **141:** 117, 1949.

[44] BLACK, A. B., AND LITCHFIELD, J. A.: Uremia complicating low salt treatment of heart failure. Quart. J. Med. **20:** 149, 1951.

[45] LEITER, L., WESTON, R. E., AND GROSSMAN, J.: The low sodium syndrome: Its origins and varieties. Bull. New York Acad. Med. **29:** 833, 1953.

[46] DANOWSKI, T. S., FERGUS, E. B., AND MATEER, F. M .: The low salt syndrome. Ann. Int. Med. **43:** 643, 1955.

[47] SIMS, E. A. H., WELT, L. G., ORLOFF, J., AND NEEDHAM, J. W.: Asymptomatic hyponatremia in pulmonary tuberculosis. J. Clin. Invest. **29:** 1545, 1950.

[48] KELLY, J. J., JR., AND DEMING, Q. B.: Low sodium syndrome and hyperpotassemia induced in edematous patients by mechanical removal of body fluid. Am. J. Med. **10:** 766, 1951.

[49] FRIEDBERG, C. K., TAYMOR, R., AND POLLAK, P.: Unpublished observations.

[50] HANENSON, I. B., GOLUBOFF, B., GROSSMAN, J., WESTON, R. E., AND LEITER, L.: Studies in water excretion following intravenous hydration and the administration of pitressin or nicotine in congestive heart failure. Circulation **13:** 242, 1956.

[51] VAN DYKE, H. B.: The regulation of water excretion by the neurohypophysis. Bull. New York Acad. Med. **29:** 24, 1953.

[52] LEAF, A., AND MAMBY, A. R.: Antidiuretic mechanism not regulated by extracellular fluid tonicity. J. Clin. Invest. **31:** 60, 1952.

[53] WELT, L. G.: Edema and hyponatremia. Arch. Int. Med. **89:** 931, 1952.

[54] SLEISENGER, M. H., AND FREEDBERG, A. S.: Ammonium chloride acidosis. Circulation **3:** 837, 1951.

[55] SCHWARTZ, W. B., AND RELMAN, A. S.: Electrolyte disturbance in congestive heart failure. J.A.M.A. **154:** 1237, 1954.

[56] SIEVERS, M. L., AND VANDER, J. B.: Toxic effects of ammonium chloride in cardiac, renal and hepatic disease. J.A.M.A. **161:** 410, 1956.

[57] WEBSTER, L. T., AND DAVIDSON, C. S.: The effect of sodium glutamate on hepatic coma. J. Clin. Invest. **35:** 191, 1956.

[58] RUBIN, A. L., AND BRAVEMAN, W. S.: Treatment of the low-salt syndrome in congestive heart failure by the controlled use of mercurial diuretics. Circulation **13:** 655, 1956.

[59] BESSMAN, A. N., AND EVANS, J. M.: The blood ammonia in congestive heart failure. Am. Heart J. **50:** 715, 1955.

[60] HAJDU, S.: Mechanism of staircase and contracture in ventricular muscle. Am. J. Physiol. **174:** 371, 1953.

[61] HERCUS, V., MCDOWALL, R. J. S., AND MENDEL, D.: Sodium exchanges in cardiac muscle. J. Physiol. **129:** 177, 1955.

[62] MCDOWALL, R. J., MUNRO, A. F., AND ZAYST, A. E.: Sodium and cardiac muscle. J. Physiol. **130:** 615, 1955.

[63] RANNEY, R. E.: Biochemical characteristics of glycerol extracted myocardial fibers. Am. J. Physiol. **183:** 197, 1955.

[64] HELLEMS, H. K., REGAN, T. J., TALMERS, F. N., CHRISTENSEN, R. C., AND WADA, T.: The mode of action of acetyl strophanthidin on the failing human heart. Abstracted, J. Clin. Invest. **35:** 710, 1956.

[65] FARBER, S. J., BECKER, W. H., AND EICHNA, L. W.: Electrolyte and water excretions and renal hemodynamics during induced congestion of the superior and inferior venae cavae of man. J. Clin. Invest. **32:** 1145, 1953.

[66] LEWIS, J. M., JR., BUIE, R. M., SEVIER, S. M., AND HARRISON, T. R.: The effect of posture and congestion of the head on sodium excretion in normal subjects. Circulation **2:** 822, 1950.

[67] LUETSCHER, J. A., JR., AND CURTIS, R. H.: Aldosterone: Observations on the regulation of sodium and potassium balance. Ann. Int. Med. **43:** 658, 1955.

[68] — AND JOHNSON, B. B.: Observations of the sodium retaining corticoid in the urine of children and adults in relation to sodium balance and edema. J. Clin. Invest. **33:** 1441, 1954.

[69] AXELRAD, B. J., CATES, J. R., JOHNSON, B. B., AND LUETSCHER, J. A., JR.: Aldosterone in urine of normal man and of patients with oedema. Brit. M. J. **1:** 196, 1955.

[70] CONN, J. W., AND LOUIS, L. H.: Primary aldosteronism. Ann. Int. Med. **44:** 1, 1956.

[71] WESTON, R. E., HANENSON, I. B., GROSSMAN, J., BORUN, E. R., ET AL.: Water retention and hyponatremia produced in edematous cardiac patients by pitressin tannate administration. Fed. Proc. **12:** 502, 1953.

[72] WHITE, A. G., RUBIN, G., AND LEITER, L.: Studies in edema. IV. Water retention and the antidiuretic hormone in hepatic and cardiac disease. J. Clin. Invest. **32:** 931, 1953.

[73] STEIN, M., SCHWARTZ, R., AND MIRSKY, I. A.: The antidiuretic activity of plasma of patients with hepatic cirrhosis, congestive heart failure, hypertension and other clinical disorders. J. Clin. Invest. **33:** 77, 1954.

ABSTRACTS

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ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

van Bogaert, A., van Genabeek, A., van der Henst, H., Vandael, J., and Arnoldy, M.: Inversion and Atypical Configuration of Unipolar Limb Leads in Right Bundle Branch Block. Arch. mal. coeur **49:** 289 (Apr.), 1956.

In experimental right bundle-branch block in dogs, direct leads from the heart show maximal positive potential of QRS in the infundibular region of the right ventricle, while wide S waves are registered at the posterior base. In the supine dog the positive potential is transmitted by the mediastinum to V_L while the S waves are transmitted through the diaphragm to V_F. It makes little difference whether the lungs are inflated, as their conductivity is poor. Horizontalization of the heart does not change the configuration of V_L and V_F until the heart apex touches the lateral chest wall, when QRS suddenly becomes negative in V_L and positive in V_F (the final part does not change direction in the illustration). Elevation of the apex 80° does not reverse the direction of QRS as in the normal heart (only the initial part of QRS is reversed in the figure). Electric connection of the left ventricle, especially of its apical portions, to the left costovertebral region causes a deep notch to appear in R of V_L and in S of V_F, while connection to this region of the right ventricle, especially in its infundibular region, causes R to become taller in aV_L and S deeper in V_F. These results, as well as the discrepancies between the anatomic and the electric position of the heart, can be explained only by assuming that the electrocardiogram depends on the projection of the total cardiac vectors on the good conductors that surround the heart (spinal column, the great vessels of the heart, the pulmonary hili and the diaphragm); of these vectors, some predominate because of a particularly favorable position with respect to these good conductors.

LEPESCHKIN

Coelho, E., De Padua, F., and Bordalo, E. S.: Electrocardiographic Alterations Induced by Cardiac Catheterization and Valvulotomy in 72 Operated Cases. Cardiologia **28:** 293 (Fasc. 5), 1956.

The authors studied electrocardiographic alterations occurring in 72 cases of mitral stenosis in the course of right heart catheterization and during and following commissurotomy. During catheterization, they observed transient development of premature beats and paroxysms of tachycardia of atrial and ventricular origin, development of bundle-branch block, shifting of the pacemaker and A-V dissociation, and beats of preexcitation contour. During the operation multifocal atrial and ventricular beats and paroxysmal tachycardia, nodal bradycardia and A-V dissociation were seen. Following surgery, atrial flutter set in or became established. S-T alterations appeared characteristic of pericarditis and preexistent signs of right heart strain and abnormalities of the P wave showed a tendency to regression.

Alterations during catheterization can be ascribed to mechanical stimulation of the endocardium and those during surgery to anesthesia, hypoxia, and mechanical irritation of the pericardium and endocardium. Postoperative alterations of the electrocardiogram can be explained on the basis of altered dynamics apart from the effects of surgical pericarditis.

PICK

Kazmeier, F., and Schild, W.: Construction of the Vector-Ballistocardiogram from Three Direct Leads. Ztschr. Kreislaufforsch. **45:** 345 (May), 1956.

In the longitudinal ballistocardiogram taken from the tibia the I wave begins 0.008 second later than in that taken from the symphysis pubis and 0.032 second later than in that taken from the sternum. The delay in the appearance of the downward movement caused by a tap on the head was 0.020 and 0.032 second respectively. At the sternum the I wave is deeper, the K wave less deep, than at the 2 other positions. As the lateral and sagittal components of the stereovector-ballistocardiogram were registered near the heart, the longitudinal component was also registered near the heart rather than at the level of the tibiae, in order to avoid conduction delay of the waves. However, practically the differences in configuration between the curves obtained with the 2 methods proved to be of little importance.

LEPESCHKIN

Koepplin, F.: The Diagnostic Value of Ballistocardiography in Angina Pectoris. Ztschr. Kreislaufforsch. **45:** 366 (May), 1956.

Of 50 patients with complaints resembling angina pectoris the electromagnetic ballistocardiogram was normal in 16 and abnormal in 13 persons who had normal electrocardiograms at rest and after exercise (100 steps). It was normal in 3 and abnormal in 2 persons with normal electrocardiograms at rest, but abnormal response to exercise. It was normal in 2 and abnormal in 14 persons with abnormal electrocardiograms at rest. A contradiction between the 2 graphic methods was accordingly present in 40 per cent, and in these cases the clinical findings nearly always supported the electrocardiographic rather than the ballistocardiographic findings.

LEPESCHKIN

Jouve, A., Corriol, J., Albouy, M., Velasque, P., and Avril, P.: Modifications of the Electric Cardiac Field at the Surface and Interior of the Thorax After Partial and Total Insulation of the Ventricles. Arch. mal. coeur **49:** 307 (Apr.), 1956.

Complete insulation of the ventricles (22 dogs) reduces the amplitude of QRS 4 to 10 times and reverses its polarity in V_R and V_L and in the upper and lower planes of circumferential unipolar thoracic leads. Intraventricular leads are not modified, while intraatrial leads become similar to V_R. Partial insulation (9 dogs) of the posterosuperior aspects of the ventricles reduces the amplitude of QRS but does not change its configuration or only leads to the appearance of a small Q wave. In anterior or lateral thoracic leads, interposition of an insulator between the heart and the electrode does not influence the configuration of the tracing appreciably. Insulation of the anterior wall does not influence the electrocardiogram if the apex remains in contact with the chest wall. After local injury, complete insulation (11 dogs) causes all S-T shifts to disappear while partial insulation (6 dogs) greatly diminishes them even when QRS is not affected. In 1 dog with right bundle-branch block complete insulation caused R to disappear but diminished the wide S only slightly.

LEPESCHKIN

Hanson, J.: The Electrocardiogram in Interatrial Communication and in Isolated Pulmonary Stenosis. Arch. mal. coeur **49:** 326 (Apr.), 1956.

Of 26 cases of atrial septal defect, the duration of P was increased in 12, and a right intraventricular conduction disturbance (wide, slurred S in leads I and V5) was present in 22 cases. The 1 case showing complete right bundle branch block had a right ventricular output of 22.4 liters per minute while the case with only a slightly elevated output (9 liters) had only a slight slurring of S. Deep inversion of T in V2 was present only in 2 cases, both of which showed marked increase in right ventricular work. The R/S ratio in V2 exceeded 1 in 13 cases, but R exceeded normal limits for the age in only 4 cases. The frontal maximal voltage of the frontal plane vector of QRS had an average value of 1.1 mV. Of 10 cases of isolated pulmonary stenosis P was elevated in 3 but did not exceed 0.10 sec. in duration and was never bifid. The QRS duration was increased only in 1 case, but in this case the S waves were not slurred. In this case, and in the four cases which showed markedly elevated R and deeply inverted T in V2, the stenotic index (systolic pressure gradient divided by the output) exceeded 10. Of the 4 cases with normal electrocardiograms, 2 had an index less than 9 and 2 were less than 13 years of age. The average amplitude of the QRS vector was 1.5 mV. The peculiarities of the electrocardiogram are important diagnostically as in many cases roentgenological findings are atypical.

LEPESCHKIN

Young, E., Wolff, L., and Karlen, W.: The Vectorcardiogram in Inferior Myocardial Infarction. IV. Am. Heart J. **52:** 232 (Aug.), 1956.

This study, based on 30 subjects, is concerned with a description of the vectorcardiogram in inferior myocardial infarction. Patients whose vectorcardiograms displayed greater than normal initial superior forces were chosen. Vectorcardiograms in which the initial rightward, anterior, and posterior forces were abnormal, and those in which the initial superior forces were oriented entirely to the left, were excluded. These features were usually associated with multiple areas of infarction, as shown by autopsy, or suggested by electrocardiography. In this series of isolated inferior myocardial infarction, abnormal superiorly oriented forces occurred in all cases during the initial stage of ventricular depolarization. This abnormality involved magnitude, direction, and duration; the normal values of these measure-

nents depend on angle α of the maximal vector in the frontal plane. Other signs of diagnostic value included the large sweep of the initial forces, their clockwise inscription, the bizarre morphologic features of the body and terminal appendage, and their slow inscription. The most characteristic abnormality of the T loop was its displacement in the negative quadrants in the sagittal and frontal planes.

RINZLER

Henig, C. R., and Tenney, S. M.: The Relationship between the Ballistocardiogram, Cardiac Movement and Blood Flow. Am Heart J. **52:** 167 (Aug.), 1956.

Animal ballistocardiograms on anesthetized dogs that were intubated and cannulated were recorded during experiments designed to alter venous return, arterial outflow, circulating blood volume, and stroke acceleration. In certain instances pure mechanical responses of the circulation were desired. To this end autonomic paralysis was obtained with hexamethonium, spontaneous respiration eliminated with curare, and denitrogenation with 100 per cent oxygen by resuscitator. Normal ballistocardiograms were found to consist of 3 major waves. The first wave is partly superimposed upon vibrations originated by atrial systole. It precedes ejection, persists in the complete absence of blood flow, and varies directly with heart size and vigor of contraction. The second is synchronous with injection and reduced to a negligible remnant by complete interruption of blood flow. The third wave is a complex of diastolic forces associated with venous flow and oscillations originated by the aortic standing wave. It is decreased by exsanguination, vasodilator drugs, outflow obstruction and air injection, and increase in hydropericardium, congestive failure, and acute vasoconstriction.

RINZLER

McKusick, V. A., Massengale, O. N., Jr., Wigod, M., and Webb, G. N.: Spectral Phonocardiographic Studies in Congenital Heart Disease. Brit. Heart J. **18:** 403 (May), 1956.

This report is concerned with an analysis of the spectral phonocardiographic findings of approximately 100 patients with many varieties of congenital heart disease.

1. Pure pulmonary stenosis (valvular type): This murmur has a Christmas-tree appearance with its peak late in systole. The loud second sound is due to aortic closure. 0.06 to 0.07 second later, a pulmonary reversal snap is present. A systolic snap shortly after the first sound is also present. Finally, an atrial gallop at the left lower sternal border or apex is frequently present.

2. Atrial septal defect: A systolic murmor may be due to relative pulmonary stenosis or tricuspid insufficiency and, in septum primum, to anomaly of the tricuspid or mitral valve. An early systolic click is due to dilatation of the pulmonary artery and is accentuated by pulmonary hypertension. A midsystolic click may be due to right ventricular hypertrophy or movements of portions of the chest wall. The apical diastolic murmur is due to a dilated right ventricle and torrential tricuspid flow. Splitting of the second sound is due to increased stroke volume of right ventricle. Rarely, splitting of the first sound occurs, due to delayed closure of the tricuspid valve.

3. Thoracic arterio-venous fistula: This murmur has a peak of intensity and frequency span in the vicinity of the second sound.

The above patterns are sufficiently distinctive to suggest the diagnosis.

Hypertension of either the systemic or pulmonary circuit does not per se produce splitting of the second sound.

A case of congenital mitral stenosis is described in which the spectral phonocardiogram was identical with that seen in most cases of rheumatic mitral stenosis.

SOLOFF

Grandell, F.: The Heart in Progressive Muscular Dystrophy. Am. J. M. Sc. **231:** 659 (June), 1956.

Using the ballistocardiograph as an indicator of myocardial function, 6 patients with progressive muscular dystrophy were examined in an effort to detect evidence of cardiac involvement. In 10 patients with onset of the disease after age 10 years, 5 showed ballistic abnormalities that could be attributed to hypertension or valvular heart disease. One of these patients with ballistocardiographic evidence of right ventricular embarrassment showed large R waves in precordial leads V_1, V_2, and V_3 in the electrocardiogram. This finding has been described in the childhood type of progressive muscular dystrophy with cardiac involvement. In 6 patients with onset of the disease before 8 years of age, abnormal ballistic traces were noted in 3 instances. In only 1 of the latter was the abnormality attributable solely to progressive muscular dystrophy. In the remaining 2 patients, the observed abnormalities were factors other than the muscular disorder. In this series it appears that dystrophic involvement of the heart muscle is uncommon, or if present, does not affect myocardial function until late in the course of the disease.

SHUMAN

HYPERTENSION

Robinson, M. J., and Williams, A.: Clinical and Pathological Details of Two Cases of Pheochromocytoma in Childhood. Arch. Dis. Childhood **31:** 69 (Apr.), 1956.

Two cases of pheochromocytoma in children are presented in this report. One boy aged 8½ years had abnormal sweating for a year, headaches for 6 months, and progressive visual changes for 1 month before being brought for medical attention. The

other child, a male of 10¾ years was brought for medical care because of increasing pallor, and abnormal sweating for some 6 months before admission. Physical examination in each showed marked elevation of systolic and diastolic pressures to heights of 180 to 200 mm./130 to 160 mm. Hg. Blood pressure elevation was sustained. Coarctation of the aorta was ruled out by physical examination. In neither case was there clinical or laboratory evidence of nephritis. Regitine tests were positive. Retroperitoneal air insufflation and angiography revealed in the first case an enlarged left adrenal gland. Results were suggestive but inconclusive in the second case of a left adrenal tumor. Exploration was carried out in both cases. Blood pressure was stabilized by the use of intravenous regitine or norepinephrine at appropriate times during manipulation of the tumors. A large adrenal tumor was removed in the first case and in the second a tumor was found at the junction of the aorta and left common iliac artery. Recovery was excellent with disappearance of symptoms and return to normal of all physical signs.

The pathology of the tumors is presented as well as a review of pheochromocytomas in children.

HARVEY

Forfar, J. O., and Kibel, M. A.: Blood Pressure in the Newborn Estimated by the Flush Method. Arch. Dis. Childhood **31:** 126 (Apr.), 1956.

The flush technic for taking blood pressures in newborn infants employs observation of the distal portion of the extremity (previously blanched by binding with a rubber bandage) for flushing when the sphygmomanometer previously inflated above arterial pressure is released slowly. Proper timing must be observed in this technic, for if the cuff is not promptly released after the blanching has been effected, the tissues are flushed by probable diffusion of blood from the deeper tissues. By this method 513 blood pressure determinations were made of 143 newborn infants ranging in age from 2 hours to 11 days. Average blood pressures in arm and leg for various ages are given ranging from a mean pressure of 59.5 mm. Hg in the arm of 7-hour-old infants to 88.3 mm. Hg in the arm of 9-day-old infants. There was no sex difference. Crying increased pressures by about 7 per cent. The blood pressure over the first 11 days increases with age and is correlated with birth weight. Comparisons of blood pressure determinations obtained by this method with the standard auscultatory methods and direct manometric recording are made.

HARVEY

Emanuel, D. A., Rowe, G. G., Musser, M. J., and Philpot, V. B., Jr.: Prolonged Hypotension with Fatal Termination after a Phentolamine (Regitene) Methanesulfonate Test. J.A.M.A. **161:** 436 (June 2), 1956.

The phentolamine (Regitine) methanesulfonate test for the diagnosis of pheochromocytoma has generally been regarded as a safe procedure. A 65-year-old woman with a proved pheochromocytoma died with ventricular tachycardia, ventricular fibrillation, and cardiac arrest after a prolonged period of hypotension following a routine phentolamine methanesulfonate test. There was cardiovascular recovery from the cardiac arrest; however, the central nervous system did not recover, and death ensued 30½ hours after the test was performed.

KITCHELL

Schapiro, S., Gordon, D. B., and Drury, D. R.: Renin Tachyphylaxis and 'Renin Hypertension' in the Rabbit. Am. J. Physiol. **185:** 543 (June), 1956.

A slow constant intravenous transfusion of renin produced a "renin hypertension." Injections of renin were superimposed until tachyphylaxis developed and blood pressure returned to control levels. Renin tachyphylaxis does not lower the pressure of renal hypertensive animals. The authors suggest that on the basis of these experiments "renin hypertension" and renal hypertension are different.

OPPENHEIMER

Poutasse, E. F., Humphries, A. W., McCormack, L. J., and Corcoran, A. C.: Bilateral Stenosis of Renal Arteries and Hypertension J.A.M.A. **161:** 419 (June 2), 1956.

It is now generally accepted that various lesions of the renal arteries and of the kidneys may cause hypertension in human beings. Severe hypertension occurred in 3 young patients (ages 14, 15, and 23 years), apparently as a sequel to bilateral stenosis of the renal arteries. In 2 the stenosis was orificial and due to fibrous intimal proliferation; in the other, the oldest patient, it was associated with severe calcific atherosclerosis of the renal artery and aorta. The 14-year-old boy and 23-year-old woman died from their disease. When the disease was recognized, in the 15-year-old boy mentioned, the obstructed segments of the renal arteries were replaced with lyophylized femoral artery homographs from an artery bank. The operations were done in stages at intervals of 2 weeks. This is the first successful arterial homografting of both renal arteries for relief of hypertension.

KITCHELL

METABOLIC EFFECTS ON CIRCULATION

Agress, C. M., Glassner, H. F., and Jacobs, H. L.: Serum Transaminase Levels in Experimental Pulmonary Infarction. Circulation Research **4:** 220 (March), 1956.

After the experimental production of pulmonary infarction in dogs the serum transaminase level was found to range from 0 to 28 units. There was no co-

relation between the amount of pulmonary infarction and the serum transaminase level. The peak serum transaminase level appeared between 12 and 23½ hours after the injury. The authors conclude that there is no evidence to indicate that acute experimental pulmonary infarction is followed by a significant elevation of the serum transaminase level.

SAGALL

Allella, A., Williams, F. L., Bolene-Williams, C., and Katz, L. N.: Role of Oxygen and Exogenous Glucose and Lactic Acid in the Performance of the Heart. Am. J. Physiol. **185:** 487 (June), 1956.

Correlation between work and oxygen use was not strict because performance of pressure-work produces different effects on oxygen use than when the heart is carrying out volume-work. At any given work load the rate of the heart plays an important role in oxygen consumption. The efficiency of this controlled heart was low. Efficiency is the ratio of work to oxygen use and a low efficiency does not necessarily mean incompetency. Availability of glucose and lactic acid depends on coronary flow. It varies with oxygen use and not with work. Consumption of exogenous glucose is related to availability but is independent of blood levels or cardiac oxygen use. On the other hand the use of exogenous lactic acid does show a positive correlation with availability, blood level, and heart oxygen use.

OPPENHEIMER

Blain, J. M., Schafer, H., Siegel, A. L., and Bing, R. J.: Studies on Myocardial Metabolism. VI. Myocardial Metabolism in Congestive Failure. Am. J. Med. **20:** 820 (June), 1956.

Coronary sinus catheterization was used to investigate the metabolism of the human heart in low output congestive failure. In comparison with normal subjects, patients with congestive failure had slightly decreased mean coronary flow and slightly elevated myocardial oxygen extraction. The oxygen consumption per 100 Gm. of heart muscle was normal. The arterial concentration of both lactate and ketones was significantly increased in patients with decompensated heart disease. Despite the elevated arterial lactate concentration, extraction of lactate by the failing myocardium was not increased. Impairment of myocardial lactate utilization was further suggested by a relative decrease in myocardial lactate extraction occurring only at high arterial lactate levels. Although these changes were only minimal in resting patients, they suggest that glycolysis may occur in the failing heart when energy demands are increased. Myocardial usage of glucose, pyruvate, fatty acids, amino acids, and ketones was not altered in the presence of compensated heart disease or frank congestive failure. Energy production per 100 Gm. of heart muscle was normal in patients with congestive failure. However, total available energy was increased because of the accompanying cardiac hypertrophy. Since the mechanical work performed was normal or decreased, the failing heart would appear to be deficient in its ability to utilize energy for effective muscular contraction. It is likely that this failure of energy utilization is the result of changes in the contractile proteins of failing heart muscle.

Both normal and failing hearts under basal conditions derive about 30 per cent of their energy requirements from carbohydrates, 5 per cent from amino acids, 7 per cent from ketones and the remainder from fatty acids. The finding of a significantly increased arterial lactate concentration in patients with congestive failure suggests that tissue oxygenation is inadequate for optimal aerobic energy production. In contrast to skeletal muscle, normal cardiac muscle is able apparently to increase its aerobic metabolism sufficiently to perform increased work, within physiologic limits, without resort to glycolysis.

HARRIS

McConahey, W. M., Owen, C. A., and Keating, F. R.: A Clinical Appraisal of Radioiodine Tests of Thyroid Function. J. Clin. Endocrinol. **16:** 724 (June), 1956.

Seven types of diagnostic radioiodine (I^{131}) tests were compared simultaneously in 92 patients with exophthalmic goiter, 46 with adenomatous goiter without hyperthyroidism, 19 with adenomatous goiter and hyperthyroidism, 13 with myxedema, 181 who were clinically normal with respect to the thyroid, and 38 who were initially suspected of having exophthalmic goiter but were later judged to be euthyroid. The 7 tests utilized were (1) 6-hour uptake (percentage of a tracer dose collected by the thyroid in 6 hours); (2) 24-hour uptake (percentage of a tracer dose collected by the thyroid in 24 hours); (3) 24-hour excretion (percentage of radioiodine excreted into the urine in 24 hours); (4) accumulation rate (the proportional rate of accumulation of radioiodine by the thyroid); (5) extrarenal disposal rate (the proportional rate of disappearance of the isotope from the blood into all organs other than the kidneys); (6) conversion ratio (proportion of radioactivity in serum that is organically bound 24 hours after a tracer dose); and (7) thyroidal iodide clearance (volume of plasma cleared of inorganic iodide by the thyroid per minute).

The most precise tests for the diagnosis of exophthalmic goiter were the 6-hour thyroidal-collection test, the thyroidal iodide-clearance test and the conversion ratio. The first is the simplest and the most rapidly performed, and required the least radioactivity; hence, it was thought the best for the requirements of a routine radioiodine test. Only 2 tests—6-hour and 24-hour thyroidal collections—were of value in the diagnosis of myxedema. None of the tests was decisive in determining whether a patient with a nodular goiter was or was not hyper-

thyroid. The basal metabolic rate and serum protein-bound iodine determinations were also done and presented in the data for reference. The serum protein-bound iodine value was also a good index for the diagnosis of exophthalmic goiter and myxedema.

MAXWELL

Burdette, W. J.: Adenosine Nucleotide Levels in Cardiac Arrest. Am. Heart J. **52:** 193 (Aug.), 1956.

The amounts of adenosine nucleotides were determined in cardiac muscle from dogs in cardiac arrest due to hypoxia that was gradually increased during a period of 1 hour or longer. When the results were compared to similar values for dogs without treatment, adenosine triphosphate, adenosine diphosphate, and adenosine monophosphate were found to be diminished significantly during cardiac arrest.

RINZLER

PHARMACOLOGY

Geffen, T. J. B., and Ross, E. J.: Potentiation of the Pressor Effect of L-Noradrenaline by Hexamethonium in Man. Clin. Sc. **15:** 271 (May), 1956.

A group of normotensive male subjects were studied. It was found that the blood pressure increases caused by norepinephrine were consistently higher after hexamethonium. The hexamethonium potentiation diminished, however, with larger doses of norepinephrine. When norepinephrine was given at a steady rate, and maximum response reached, intravenous injection of hexamethonium resulted in a sharp increase in pressure. Atropine subcutaneously also potentiated the pressor response to norepinephrine.

The mechanism of potentiation is presumed to be due to blockade of buffer nerves that normally counteract pressure rises. There is experimental evidence indicating that it is not due solely to vagal inhibition.

ENSELBERG

Fawaz, G.: Effect of Quinidine, Procaine Amide and Mersalyl on Lethal Dose of Ouabain in Isolated Dog Heart. Proc. Soc. Exper. Biol. & Med. **88:** 654 (Apr.), 1955.

A study was done on the effect of quinidine, procaine amide, and mersalyl (a mercurial), singly and in combination with lethal doses of ouabain in the intact dog and dog heart-lung preparations. The myocardial depression produced by quinidine could be counteracted with ouabain. Quinidine, in relatively large doses, neither decreased nor increased the dose of ouabain that produced ventricular fibrillation. This finding was in harmony with the results of Weiss and Hatcher obtained with intact cats. Furthermore, quinidine alone, under the conditions of Fawaz's experiment, produced no premature ventricular beats, ventricular tachycardia, or ventricular fibrillation in intact dogs or isolated hearts. Procaine amide depressed the myocardium to a much lesser extent than quinidine, but in large doses it produced ventricular ectopic rhythms. Yet even these arrhythmia-producing doses of procaine amide did not influence the lethal dose of ouabain. The same was true of the mercurial. It was concluded that under the conditions of this experiment, it would appear that the arrhythmia-producing properties of different drugs are not necessarily additive and that the danger of producing ventricular fibrillation by the combination of such drugs is perhaps exaggerated.

MAXWELL

Dohrmann, R., and Engelking, R.: Comparative Studies on the Myocardial Action of Some Digitalis Glycosides and Digitaloids in the Heart-Lung Preparation. Arch. Kreislaufforsch. **23:** 271 (Dec.), 1955.

In 55 heart-lung preparations in dogs, heart failure was produced by increasing the venous pressure. The average maximal increase of heart output was 22 per cent and appeared on the average 28 minutes after digitoxin. It was 24 per cent (9 min.) after "digipurat," 14 per cent (20 min.) after acetyldigitoxin, 16 per cent (12 min.) after lanatoside C, 30 per cent (16 min.) after strophanthin k, 15 per cent (5 min.) after convallatoxin, and 18 per cent (15 min.) after "scillaren." The toxicity of a preparation seemed to be inversely proportional to the time of appearance of the maximal effect.

LEPESCHKIN

Moyer, J. H., Ford, R., Kinard, S., and Dennis, E.: Management of Some Problems in the Use of Newer Cardiovascular Drugs. Texas J. Med. **52:** 293 (May), 1956.

Problems associated with the use of some recently released cardiovascular drugs were reviewed. The drugs discussed included 2 diuretics—neohydrin and diamox; and antihypertensive drugs, namely rauwolfia compounds, hydralazine, various ganglionic-blocking agents, and veratrum. The side effects of these drugs were presented in some detail, together with consideration of the therapeutic indications and results.

Neohydrin is an effective oral diuretic when given in adequate dosage (4 to 8 tablets daily). When used in adequate amounts 25 per cent of patients complain of gastrointestinal symptoms, and the drug must be discontinued in about 10 per cent of patients who take it. Occasionally dermatitis and stomatitis are seen during Neohydrin administration. Diamox is considered inadequate for control of severe heart failure when used alone. Since it produces its effect by creating a temporary acidosis, its administration to patients with renal failure and associated heart failure may be disastrous. The side

effects of rauwolfia compounds include most frequently nasal congestion, which, however becomes less severe with prolonged administration. Weight gain is seen in approximately 50 per cent of patients on rauwolfia derivatives, apparently directly related to increase in appetite. Increasing frequency of bowel movements without diarrhea, mild dizziness (nonpostural), excessive sedation, weakness, fatigue, agitated depression, and nightmares are also side effects of the rauwolfia preparations. The most bothersome side effects of hydralazine are tachycardia and headache due to the direct stimulant effects on the heart. These effects are less marked when hydralazine is given in combination with rauwolfia. The majority of the side effects of the ganglionic-blocking agents are due to blockade of the parasympathetic ganglions. These effects include dizziness and syncope due to excessive reduction in blood pressure, constipation and paralytic ileus (counteracted by prostigmine and cathartics). The ganglionic-blocking agents alone or in combination with other antihypertensive drugs may be effective agents, particularly in the treatment of malignant hypertension. Untoward reactions from the veratrum alkaloids are primarily due to the marked fall in blood pressure that may be produced.

The undesirable effects associated with all these agents may be minimized by careful attention to the proper indications for use of a drug, by individualization of dosage for each patient, and by better understanding of the pharmacodynamics of the drug administered.

MAXWELL

Modell, W.: Recent Contributions to Diuretic Therapy. Am. J. M. Sc. **231:** 564 (May), 1956.

Diuretic drugs are applied primarily in the relief of edema associated with heart failure, ascites of cirrhosis, nephrotic syndrome, and the edema of pregnancy. Specialized uses include the treatment of glaucoma, bromide intoxication, epilepsy, premenstrual edema, and localized edema. Retention of sodium and water are the disturbances leading to edema in heart failure and certain other conditions mentioned. Changes in the renal hemodynamics and hormonal alterations associated with these disorders are among the important factors related to electrolyte and fluid retention. Refractory edema may be associated with electrolyte disturbances or hypoproteinemia. Among the agents discussed in this review are aminophylline, resins, ammonium chloride, Diamox, cortisone and ACTH, peritoneal dialysis, Southey-Leech tubes, low-salt diets, and salt-poor albumin. The mercurial diuretics maintain a position of eminence in this field, operating by means of inhibition of enzymes essential for specific ion resorption in the renal tubule. The mode of action has been assigned by various workers to both proximal and distal renal tubule. The pharmacology, side effects, and therapeutic actions of these agents in the clinical conditions enumerated are thoroughly recounted. The oral mercurials and nonmercurial diuretics such as Mictine, isocytosines, and other miscellaneous agents are also discussed in this extensive and comprehensive review.

SHUMAN

Nolke, A. C.: Severe Toxic Effects from Aminophylline and Theophylline Suppositories in Children. J.A.M.A. **161:** 693 (June 24), 1956.

Toxic effects resulting from oral and intravenous use of aminophylline and theophylline are well known, but reactions to rectal administration have received scant attention in the past. Thirteen cases of severe toxic reaction to theophylline given rectally are reported with 4 deaths. The rectal suppository seems a poor means of theophylline or aminophylline administration because the unpredictability of absorption makes a fixed therapeutic regimen dangerous.

KITCHELL

PHYSIOLOGY

Popper, H. L., Jefferson, N. C., and Necheles, H.: Blocking of the Intrahepatic Blood Circulation. II. Am. J. Physiol. **185:** 125 (Apr.), 1956.

The phrenic arteries can maintain the liver when the hepatic artery and portal vein are tied. If the intrahepatic branches of the hepatic artery are blocked necrosis is produced. No comparable necrosis resulted when the intrahepatic branches of the portal vein were similarly obstructed. The essential collateral vessels are via the hepatic artery.

OPPENHEIMER

Adelman, W. J., Jr.: The Effect of External Calcium and Magnesium Depletion on Single Nerve Fibers. J. Gen. Physiol. **39:** 753 (May 20), 1956.

The effect of calcium and magnesium depletion in crustacean single nerve fibers was investigated. Three different motor axons found in the walking legs of the lobster were used in the preparations: (1) the opener fiber, (2) the slow closer fiber, and (3) the fast closer fiber. All types of fibers became more excitable in calcium-free solutions. However, only the opener fiber showed spontaneous activity. After 5 minutes in the calcium-free solution all fibers showed a rise in rheobase value and more rapid accommodation. Magnesium ion acted synergistically with calcium ion. All types of nerve fibers became spontaneously active when solutions were deprived of both calcum and magnesium. Whenever fibers were exposed to calcium- and magnesium-depleted solution for longer than 5 minutes, extreme depressions of excitability resulted.

BROSTOFF

Froment, R., Jourdan, F., Gonin, A., Bruel, P., and Mornex, R.: Experiments on Physiological and Pathological Neuro-Coronary and Viscero-Coro-

nary Correlations. Arch. mal. coeur **49:** 201 (Mar.), 1956.

Esophageal distention reversed the polarity of the T wave in 1 of 6 normal dogs and in 3 of 16 dogs with ligated anterior descending coronary arteries. Distention of the biliary duct caused these changes in all of 3 normal dogs, in 3 of 8 dogs with coronary ligation, and in 2 of 4 dogs with the descending coronary injected with sodium ricinoleate. Stimulation of the 3 first cervical nerves caused these changes in 1 of 12 normal dogs, in 4 of 12 dogs with coronary ligation, and in 2 of 4 dogs with coronary injection. It is concluded that while coronary reflexes can be elicited by all kinds of nervous stimulation, they are very inconstant even in animals with impaired coronary circulation.

LEPESCHKIN

Bär, C. G., Zeilhofer, R., and Heckel, K.: Chronic Anemia and Its Repercussions on Heart and Circulation. Ztschr. Kreislaufforsch. **45:** 439 (June), 1956.

One hundred and thirty-seven cases of anemia were subdivided into the following groups: I (hemoglobin 20–40 per cent), II (Hemoglobin 41–60 per cent), and III (hemoglobin 61–80 per cent). The average heart rate was 86.5 in group I, 86.1 in II, and 74 in III. The heart rate accordingly is not a measure of the degree of anemia, once hemoglobin has become less than 60 per cent. Systolic murmurs were present in 54 per cent of group I, 42 per cent of II, and 24 per cent of III. Roentgenologic enlargement of the heart was found in 51 per cent of group I, 36 per cent of II, and 15 per cent of III. Sixty-eight per cent of the enlarged hearts showed a murmur. Abnormal electrocardiograms (usually T and S-T changes) were present in 67 per cent of group I, 52 per cent of II, and 16 per cent of III.

LEPESCHKIN

Rowe, G. G., Huston, J. H., Weinstein, A. B., Tuchman, H., Brown, J. F., and Crumpton, C. W.: The Hemodynamics of Thyrotoxicosis in Man with Special Reference to Coronary Blood Flow and Myocardial Oxygen Metabolism. J. Clin. Invest. **35:** 272 (March), 1956.

Studies on patients with thyrotoxicosis indicate that, contrary to previously published observations, the myocardium participates in the increase in oxygen consumption which is characteristic of all tissues in thyrotoxicosis. This hypermetabolism is accompanied by an increase in coronary blood flow, and in oxygen consumption per beat, but by a decrease in coronary vascular resistance. After treatment (with radioactive iodine in all but 1 who had subtotal thyroidectomy), the cardiac output and work, the coronary blood flow, and the myocardial oxygen consumption returned to normal, and the coronary vascular resistance increased.

WAIFE

Attinger, E. O., Herschfus, J. A., and Segal, M. S.: The Mechanics of Breathing in Different Body Positions. II. In Cardiopulmonary Disease. J. Clin. Invest. **35:** 912 (Aug.), 1956.

Various respiratory physiologic studies were performed in 12 subjects with chronic pulmonary emphysema and in another group with various cardiopulmonary diseases. The results were studied in the supine, sitting, prone, head-down, and lateral positions. The over-all changes in the mechanics of breathing in these various physical positions for both groups of patients were essentially the same as for a normal group previously studied. Two special measurements were made: (1) the compliance, which is the volume change per unit pressure change expressed as liters per centimeter of water, and (2) mechanical resistance, which is the pressure necessary to obtain a given flow rate expressed in centimeters per liter per second. The normal subjects did not show any change in compliance or resistance with an increase in respiratory rate. The chronic pulmonary emphysema group, however, showed a marked drop of compliance with an increase in rate in all positions. Their resistance values remained essentially the same. The group with various cardiopulmonary diseases showed a significant drop of compliance in the supine and prone positions, a significant drop of inspiratory resistance in the supine, and of expiratory resistance in the sitting and supine positions.

WAIFE

Kelly, W. D., and Visscher, M. B.: Effect of Sympathetic Nerve Stimulation on Cutaneous Small Vein and Small Artery Pressures, Blood Flow and Hindpaw Volume in the Dog. Am. J. Physiol. **185:** 453 (June), 1956.

Electric stimulation of the lumbar sympathetic chain caused a rise from 17 to 30 mm. Hg in small cutaneous veins. After stimulation there was a further rise to 42 mm. Hg. The small cutaneous saphenous artery was observed to change from a pressure of 99 mm. to 138 mm. Hg. However, in this case there was a fall to 55 mm. Hg after stimulation was stopped. Volume of the hind paw and flow in the saphenous artery were sharply decreased by stimulation of the sympathetic nerves. Since pressure is increased in small veins and blood flow is decreased, an increased resistance to flow of blood out of the venous bed is indicated. Both small veins and arteries of the skin of the dog's hind paw constrict in response to activity in their sympathetic nerves. A large rise in intraluminal pressure results. Small veins and arteries may respond independently.

OPPENHEIMER

Guyton, A. C. and Greganti, F. P.: A Physiologic Reference Point for Measuring Circulatory Pressures in the Dog—Particularly Venous Pressure. Am. J. Physiol. **185:** 137 (April), 1956.

Dogs were rotated into all positions in space. In this manner the axes of rotation that produced the least change in right atrial pressure were determined. This point of reference for measuring circulatory pressures is in the lower portion of the right ventricle. The point is very precise from one animal to another, and is not influenced by the condition of the circulation. The heart controls the end diastolic pressure of the right ventricle because an increase in this value increases output and thus the end diastolic pressure returns toward normal.

OPPENHEIMER

Rose, D. J., Bader, M. E., Bader, R. A., and Braunwald, E.: Catheterization Studies of Cardiac Hemodynamics in Normal Pregnant Women with Reference to Left Ventricular Work. Am. J. Obst. & Gynec. **72:** 233 (Aug.), 1956.

Data on cardiac hemodynamics as studied by cardiac catheterization in 46 normal pregnant women were presented. Observations were made both at rest and during the stress of exercise. There was an increase in cardiac output at rest observed in the earliest period of gestation studied (fourteenth to twenty-fourth weeks) reaching a maximum of 40 per cent greater than that in nonpregnant control women at the twenty-fifth to the twenty-seventh weeks of pregnancy, then falling progressively to normal just prior to term. This was accomplished by a reciprocal change in arteriovenous oxygen difference, while oxygen consumption was only slightly increased. The cardiac output response to exercise was normal in terms of increase in output per unit increase in oxygen consumption in all groups. This indicates that there was no impairment in myocardial reserve. The only remarkable change in pressures in the right heart or pulmonary artery was in the right ventricular end-diastolic pressure, which was elevated in 5 of 26 patients at rest and in 10 patients on exercise during the twenty-fifth to the thirty-fifth weeks of gestation. Total peripheral resistance was reduced from the fourteenth to the thirtieth week of pregnancy, returning to normal prior to term. Left ventricular work was elevated between the fourteenth and the thirtieth weeks of gestation, and fell prior to parturition. While the exact mechanism responsible for the alterations observed cannot be defined from the data presented, several possibilities to explain the increased cardiac output were discussed. These data on normal pregnant women may be used as criteria for the physiologic evaluation of the pregnant patient with heart disease. It is hoped that this information will provide a more quantitative approach to the problem of selection of such patients for surgery on the mitral valve, therapeutic abortion, and postdelivery sterilization.

MAXWELL

Drischel, H.: Effect of Intravenous Glucose Injections on the Blood Pressure. Ztschr. Kreislaufforsch. **45:** 568 (Aug.), 1956.

In 18 normal persons rapid intravenous injection of 0.2 Gm. of glucose per Kg. of body weight (40 per cent solution), decreased the systolic pressure 10 to 15 mm. for several hours, while the diastolic pressure showed only a minimal decrease. These changes were greater if the resting blood pressure was high. The heart rate decreased slightly. This is considered as a parasympathicotropic reaction.

LEPESCHKIN

Moreira, M. F., Mottram, R. F., and Werner, A. Y.: The Effect of Venous Pressure on the Oxygen Content of Venous Blood in the Deep Forearm Veins. J. Physiol. **133:** 255 (Aug.), 1956.

During a 4-minute period of venous congestion of the human forearm at 60 mm. Hg, an initial rise, followed by a fall, occurs in the oxygen content of blood withdrawn from the deep veins. Venous blood withdrawn during periods when the cuff is alternately inflated and deflated at 5 to 15 second intervals may contain up to 2 volumes per cent more oxygen than during the control period. The vascular dilatation postulated as occurring during venous occlusion must be such that blood flows from artery to vein through shunt channels and not through capillaries.

AVIADO

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Zimmermann, B., Casey, J. H., and Bloch, H. S.: Mechanisms of Sodium Regulation in the Surgical Patient. Surgery **39:** 161 (Jan.), 1956.

The authors presented evidence from the literature to indicate that adrenal hyperactivity exists in the postoperative state and that the internal distribution and the external balance of sodium ion are radically altered by major surgical operations.

Experiments were performed which suggested that specific endocrine mechanisms were responsible for the positive balance of sodium, characteristic of the postoperative state, and that these mechanisms operated independently of the anterior pituitary. The authors also found that a substance resembling aldosterone was consistently increased in the urine of patients immediately following surgery.

ABRAMSON

Davis, J. O., Howell, D. S., Goodkind, M. J., and Hyatt, R. E.: Accumulation of Ascites during Maintenance of Adrenalectomized Dogs with Thoracic Inferior Vena Cava Constriction, on a High Sodium Diet without Hormone Therapy. Am. J. Physiol. **185:** 230 (Apr.), 1956.

Dogs were prepared in which both adrenal glands were removed and the thoracic inferior vena cava was constricted. These dogs developed ascites and

were maintained on 160–240 mEq. per day of sodium, which is a high regimen. There was no replacement therapy. Successful maintenance required the use of sodium citrate in the high-salt diet to prevent acidosis. When the sodium balance was positive (ingested sodium greater than that excreted by kidneys) sodium was retained and ascites accumulated. The authors stress the importance of the role of the adrenal cortex in the formation of ascites, since a large sodium intake is needed to exceed the high rate of renal sodium loss.

OPPENHEIMER

Poppell, J. W., Vanamee, P., Roberts, K. E., and Randall, H. T.: The Effect of Ventilatory Insufficiency on Respiratory Compensations in Metabolic Acidosis and Alkalosis. J. Lab. & Clin. Med. **47:** 885 (June), 1956.

The degree of respiratory compensation in metabolic acidosis was demonstrated graphically by 99 determinations in acidotic patients with normal respiration. This compensation was always incomplete at low levels of total carbon dioxide. In the presence of respiratory insufficiency for carbon dioxide elimination, the expected lowering of partial pressure of carbon dioxide was not attained and pH changes were therefore excessive. Thirty determinations in metabolic alkalosis and respiratory insufficiency were compared with the previously published points from alkalotic patients with normal respiration. In patients with normal respiration, respiratory compensations in metabolic alkalosis were minimal; however, in the patient with respiratory insufficiency, markedly elevated levels of total carbon dioxide were more frequently encountered than in the patient with normal respiratory exchange. From the data presented it was also evident that in the assessment of compensatory mechanisms in acidosis or alkalosis, it is important to determine the presence of respiratory insufficiency if erroneous conclusions are to be avoided.

MAXWELL

Houck, C. R.: Sodium, Potassium and Nitrogen Balances in Chronic Nephrectomized Dogs. Am. J. Physiol. **185:** 175 (Apr.), 1956.

In this study totally nephrectomized dogs were maintained on a low-salt, low-calorie diet by peritoneal dialysis intermittently. Sodium balance was achieved, but that of potassium and nitrogen was not. Potassium balance was negative even though the dialysate contained this element up to 3.7 mEq. per L. Loss of plasma protein and red cells into the fluid used in the peritoneal cavity may explain the negative potassium and protein balances. Hypertension developed even though potassium and protein were lost and sodium was not retained.

OPPENHEIMER

Johnstone, P. N., Stone, R. G., Burdick, H. C., Allebach, H. K. B., Patton, F. E. T., and Erb, L. E.: Studies on the Etiology and Treatment of Acute Renal Failure. J.A.M.A. **161:** 491 (June 9), 1956.

The serious nature of acute kidney failure is generally recognized. The importance of accurate records in this situation is emphasized by experiences in the United States Army during World War II and in the Korean conflict. As late as the start of the Korean War, approximately 90 per cent of the wounded men who developed renal failure died. A special center for the treatment of renal insufficiency was established in the combat zone of Korea and emphasis was placed on early recognition and treatment of renal failure. The mortality rate per patient for this condition fell promptly to approximately 50 per cent. This figure was not reduced further even though the chemical effects of uremia responded to methods of treatment then available. It is now thought that anuria before death is caused by renal ischemia secondary to intense renal vasoconstriction. It should be correctible by the vasodilating action of papaverine. The authors found no other drug equaling papaverine hydrochloride for this purpose. By critical study it was found that relaxation of vasospasm and reversal of renal failure occurred after only a small amount of papaverine was given. They preferred to treat the average patient having acute kidney failure with 0.5 gr. (32 mg.) of papaverine hydrochloride given by intramuscular injection every 2 hours for about 48 hours. Eleven patients with acute renal failure were treated. Ten promptly developed material increases in urinary output. The 1 patient who did not respond was shown to have purulent material in many of the renal tubules and marked infiltration with inflammatory cells and the primary condition was not renal ischemia. In acute renal failure caused by ischemia prompt positive efforts should be made to improve the blood supply of the kidneys with the administration of papaverine hydrochloride.

KITCHELL

Tobian, L., and Fox, A.: The Effect of Nor-Epinephrine on the Electrolyte Composition of Arterial Smooth Muscle. J. Clin. Invest. **35:** 297 (March), 1956.

Samples of arterial wall were obtained before and during the infusion of norepinephrine in dogs. The samples were then analyzed for electrolytes. The femoral artery wall invariably lost potassium under the influence of norepinephrine. Control dogs, that received saline infusions, showed an average increase in the potassium content of the arterial wall. There was some gain in sodium in the norepinephrine dogs, but this was not consistently found. It was also curious that this finding was in contrast to the gain in potassium in the arterial wall of rats with renal or desoxycorticosterone hypertension. The authors make the interesting speculation that the loss of potassium from arterial smooth muscle may be

important in the chain of events associated with arterial contraction induced by norepinephrine.

WAIFE

RHEUMATIC FEVER

Greenman, L., Weigand, F. A., Mateer, F. M., and Danowski, T. S.: Cortisone Therapy of Rheumatic Fever: Relation of Clinical Response to Levels of Serum Protein-Bound Iodine, Serum Corticoids and Urinary 17-Ketosteroids. J. Clin. Endocrinol. **16:** 634 (May), 1956.

Treatment of children with initial or recurrent attacks of rheumatic carditis with cortisone or corticotropin resulted in a drop in serum protein-bound iodine level; a rise in serum corticoid level; an increase in urinary output of 17-ketosteroids; and rarely any significant decrease in the eosinophil count, which was already low prior to therapy. The rise in urinary neutral 17-ketosteroids was greater following oral than intramuscular cortisone. Corticotropin in large doses for 3 to 6 days at the end of cortisone treatment did not maintain this rise. Following the oral administration of steroid, peak values were recorded in the serum at 1 hour; high values, though at a decreased level, were still present at 6 hours.

The studies indicated that neither the presence of these changes nor their intensity had any relationship to the clinical outcome, i.e., there was no correlation of these factors with ultimate resolution or nonresolution of the carditis.

MAXWELL

Green, M. R., and Wile, R.: The Value of Pediatric Psychiatric Teamwork in the Treatment of Rheumatic Fever. Pediatrics **17:** 757 (May), 1956.

A report of the 1-year program carried out at Roosevelt Hospital in New York City by the Psychiatric Service among children with rheumatic fever is presented. The value of the program is pointed up by 4 excellent case histories. The emotional changes produced by prolonged bed rest and frequent injections are elaborated. The results of close teamwork among the pediatricians, nurses, social workers, families, and psychiatrists in helping the children adjust to their illness, its limitations on physical activity, and prolonged convalescence appear to be quite worth the effort of the elaborate program of therapy. By this report the authors hope to stimulate such treatment at other institutions.

HARVEY

Wilson, M. G., and Lim, W. N.: Natural Course of Active Rheumatic Carditis and Evaluation of Hormone Therapy. J.A.M.A. **160:** 1457 (April 28), 1956.

One hundred records, starting from the most recent, were arbitrarily drawn for analysis from the active files of the cardiac clinic of the New York Hospital, Cornell Medical Center. The only selective factor was an observed attack not treated with hormones. These records were compared with those of 55 patients with active carditis of 3 to 21 days' duration who were given hormone therapy between 1949 and March 1955. In all these cases a diagnosis of carditis was made on the basis of the following signs and symptoms: (1) poor or distant heart sounds (tachycardia, gallop rhythm), (2) friction rub, (3) new and changing murmurs (systolic or diastolic), (4) increasing enlargement of heart on physical and fluoroscopic examinations, (5) diminishing cardiac reserve, (6) congestive failure, and (7) electrocardiographic abnormalities. The hormones used included corticotropin, cortisone, or hydrocortisone. Only 1 was used in a given case and all seemed to be equally effective. The average duration of therapy was 7 days. Hormones were administered every 6 hours as follows: corticotropin intramuscularly, 25 units for 4 days and 20 units for 3 days, in total daily amount of 80 to 100 units; cortisone orally, 100 mg. for 4 days and 80 mg. for 3 days, in total daily amount of 320 to 400 mg.; hydrocortisone orally, 80 mg. for 4 days and 60 mg. for 3 days, in total daily amount of 240 to 320 mg. The analysis of the course of active rheumatic carditis in patients receiving symptomatic therapy during the years 1930 to 1955 revealed no significant difference in the pattern of rheumatic fever over this 25-year period. The average duration of carditis was less than 1 month in only 20 per cent, 2 to 4 months in 30 per cent, and more than 4 months in 50 per cent. Residual cardiac damage was present in every patient. In the patients receiving hormone therapy 3 to 21 days after onset of illness for an average period of 7 days the duration of active carditis was less than 1 month in 69 per cent, and less than 2 months in 31 per cent. In 84 per cent of the patients treated whose attacks were initial, there was no evidence of residual damage. The course of carditis in patients receiving hormone therapy is markedly shortened in contrast to that of the control group, both in duration and extent of residual cardiac damage. This is attributed to administration of adequate hormone therapy before irreversible damage was sustained.

KITCHELL

SURGERY AND CARDIOVASCULAR DISEASE

Sanger, P. W., Taylor, F. H., Matsuba, T., and Salomone, F.: The Use of Artificial Fiber as an Artery Substitute. Ann. Surg. **143:** 862 (June), 1956.

The past decade has seen rapid strides in the advancement of vascular surgery. The treatment of segmental arterial diseases by excision and insertion of various types of grafts has been successful in the hands of many surgeons. Arterial homografts have been more commonly used. The difficulty in obtain-

ing and processing such grafts and the degenerative changes sometimes noted have led to a search for a more satisfactory substitute.

The authors have performed experimental artificial arterial grafts on the thoracic aortas of 83 dogs and have found that knitted, seamless Orlon grafts function well and are readily available, inert, and nonirritating. Autopsies performed from a few weeks to 18 months after surgery showed, grossly and microscopically, a smooth fibrous tissue layer inside the lumen of the graft, as well as the growth of fibrous tissue outside through the interstices of the graft. Aortograms made at varying postoperative intervals showed patent grafts without dilatation or significant constriction. Knitted, seamless Orlon fabrics have been used successfully as arterial grafts at various levels of the aorta and the iliac arteries by 24 surgeons throughout the country on 78 patients.

Although knitted Orlon or Nylon is a satisfactory prosthesis for the aorta and common iliac arteries, the smaller arteries present a different problem, and results have, in general, been discouraging. Teflon, a new synthetic fabric, has promising possibilities in peripheral vessels.

MAXWELL

Bellman, S., and Göthman, B.: The Viability of Experimental Aortic Grafts, and Its Influence on the Functional Result of Transplantation. Angiology **7:** 89 (Apr.), 1956.

The behavior of variously treated canine aortic transplants was examined to establish whether viability was a requisite for a good functional result. The types of grafts used included autogenous material, homologous material stored in nutrient fluid, homologous frozen and homologous formalinized grafts. Viability was measured by the capacity of the graft to incorporate radiosulfate. Viability was found to be highest among the autogenous grafts, but a good functional result was not dependent on the presence of living material in the transplants.

WESSLER

Creech, O., Jr., De Bakey, M. E., and Cooley, D. A.: Surgical Treatment of Dissecting Aneurysm of the Aorta. Texas J. Med. **52:** 287 (May), 1956.

The authors discuss dissecting aneurysm of the aorta from the standpoint of incidence, pathology, and pathogenesis, clinical and roentgenographic manifestations, diagnosis, prognosis, and treatment. Only about 10 per cent of patients with dissecting aneurysm of the aorta survive for a significant period of time, the majority dying within hours or days after onset of symptoms. Surgical therapy is directed toward preventing further dissection and rupture, and the restoration of normal blood flow. Characteristically, dissection of the aorta begins just above the aortic valve or just beyond the left subclavian artery. When dissection begins in the ascending aorta, a reentry passage into the true aortic lumen is created with obliteration of the false lumen below. When dissection begins at the left subclavian artery, excisional therapy with homograft replacement may be employed. Rarely with the more acute forms of dissection, excision with lateral aortorrhaphy may be utilized. Of 13 cases of dissecting aneurysm, 4 were treated by creation of a reentry passage, and in 9 excisional therapy was employed. There were 3 deaths following the operation and 10 survivals with symptomatic relief and reduction of the threat of further dissection.

MAXWELL

Kenny, S.: Value of "Hibernation" in Severely Shocked Patients. Brit. M. J. **1:** 211 (July 28), 1956.

In 3 elderly patients, severely shocked as a result of the condition for which surgery was indicated, pronounced improvement accompanied hibernation and surgery was possible. The first patient, age 60, had a perforated peptic ulcer; the second, age 82, perforated colonic diverticulum; the third, age 63, a ruptured abdominal aneurysm. The author thought that hibernation blocked the sympathetic nervous system, relieved vasoconstriction, and improved cerebral and other tissue oxygenation. She points out the necessity for slow induction of hypothermia with careful observation of blood pressure and with fluid replacement to keep step with the enlargement of the vascular bed. The course of anesthesia and the postoperative progress was remarkably smooth in these patients.

MCKUSICK

de Gaudart d'Allaines, F., Mouquin, M., Hatt, P.-Y., Sauvan, R., Fanjoux, J., and Latscha, B.-I.: Plastic Operation of a Cardiac Aneurysm. Electrocardiographic Study During the Operation. Arch. mal. coeur **49:** 193 (Mar.), 1956.

In a patient with myocardial infarction in whom a ventricular aneurysm with marked systolic expansion developed within 6 weeks of the infarction, the aneurysm was covered with a piece of pectoral muscle to prevent further expansion of the aneurysm. During the operation, carried out 5 months after the infarction, direct unipolar leads were taken from the heart through the adherent pericardium. In leads V_2 to V_6 as well as in the direct leads corresponding to them, absence of R, slight elevation of S-T and deep, pointed inversion of T were seen. However, the lead from the midpoint of the aneurysm showed depressed S-T and inverted T waves of much greater voltage than in the corresponding precordial lead.

LEPESCHKIN

Longmire, W. P., Jr., Smith, R. T., McEachen, J. A., Adams, F. A., and Young, W. W.: Interatrial Septal Defects. Arch. Surg. **72:** 863 (May), 1956.

The authors reviewed the clinical results obtained in a series of 34 patients with interatrial septal defects treated surgically, using several different approaches.

Among the criteria that were considered important as indications for surgical intervention were disabling or progressive symptoms, usually fatigability or dyspnea, evidence of pulmonary hypertension or a left-to-right intracardiac shunt of considerable magnitude, x-ray evidence of cardiac enlargement, signs of right ventricular strain, and a history of recurrent episodes of upper respiratory tract infections.

Eleven of the defects were successfully closed by the atrial-well technic, 15 by the atrioseptopexy method, and 4 by the "open" technic utilizing cardiac inflow and outflow, occlusion, and hypothermia. Two deaths occurred during operation. The postoperative results were considered clinically satisfactory in 20 patients. According to the authors, atrioseptopexy is the easiest and least hazardous procedure. It is best adapted for closure of the small or moderate-sized centrally located defect.

ABRAMSON

ROENTGENOLOGY

Moros, G., Villagordoa, G., Neri, R., Dorbecker, N., and Legault, G.: Fluorodensography with Radio-Opaque Substances—A New Method of Hemodynamic Study. Arch. mal. coeur **49:** 250 (Mar.), 1956.

In postinspiratory apnea, 10 ml. of 70 per cent Diodrast are injected rapidly into the right cubital vein, the beginning and end of the injection being marked on the electrokymogram from the middle of the right or left ventricle. In 19 normal persons the average interval from the midpoint of injection to the first fall of the electrokymographic curve of the left ventricle was 5.61 seconds with a standard deviation of 0.59 second; the corresponding interval for the right ventricle was 1.63 seconds with a standard deviation of 0.23 second. The difference between these values, corresponding to the pulmonary circulation time, averaged 3.98 seconds with a standard deviation of 0.61 second. In normal subjects only the systolic but not the diastolic level falls, while in pathologic cases both levels fall. The change in the right ventricle is much more pronounced and abrupt than in the left ventricle. No incidents occurred during the test, and only 3 cases had a transient painful sensation in the right shoulder.

LEPESCHKIN

Stauffer, H. M., Durant, T. M., and Oppenheimer, M. J.: Gas Embolism. Roentgenological Considerations, Including the Experimental Use of Carbon Dioxide as an Intracardiac Contrast Material. Radiology **66:** 6868 (May), 1956.

The above is a report on clinical and experimental air embolism, and the differentiation of venous (pulmonary) from arterial embolisms, the former amenable to emergency therapy, the latter usually rapidly fatal. Obstruction of right ventricular outflow is often complicated by air or gas emboli in smaller pulmonary arteries. Mortality is reduced in the left decubitus position.

Experimentally, carbon dioxide being 20 times as soluble in serum as air or oxygen, can be injected with relative safety, thus permitting valvular and cardiac chamber visualizations, *including valves.* Many dogs and 2 infants safely tolerated intravenous injection of 7.5 ml. of carbon dioxide per Kg. of body weight.

SCHWEDEL

Keats, T. E., Kreis, V. A., and Simpson, E.: The Roentgen Manifestations of Pulmonary Hypertension in Congenital Heart Disease. Radiology **66:** 693 (May), 1956.

The authors surveyed roentgen criteria for the detection of pulmonary hypertension such as, total cardiac enlargement, right ventricular enlargement, pulmonary artery enlargement, perihilar vessel enlargement, relative narrowing of pulmonary arteries, tortuosity of peripheral pulmonary arteries, and Kerley lines, in relation to 36 patients with congenital heart disease and pulmonary hypertension. Only the disparity in size of proximal and peripheral pulmonary vessels was found to be useful. Pulmonary venous dilatation was frequently found in left-to-right shunts, but was not present when the shunt was from the right to the left. There was no consistent relationship between the presence of Kerley lines and pulmonary hypertension. Right ventricular and pulmonary outflow tract enlargement occur in the presence of left-to-right shunts without pulmonary hypertension, and therefore, are not reliable for use as indications for the presence of pulmonary hypertension. The degree of enlargement appears to correlate more closely the magnitude of pulmonary blood flow.

SCHWEDEL

Celis, A., Cicero, R., Del Castillo, H., and Arce, A. G.: Temporary Arrest of the Contrast Medium in Angiocardiography. Acta. Radiol. **45:** 341 (May), 1956.

The authors investigated the effects of the Valsalva maneuver in trained normal personnel to determine its effects on blood flow in the venae cavae, cervical and azygos veins, right atrium, right ventricle, and the pulmonary artery. The Valsalva maneuver causes an expiratory contraction of the thoracic wall on overdistended lungs after maximal inspiration, and results in a considerable increase in intrathoracic pressure. Angiocardiograms obtained during this procedure reveal a diminution in the caliber of the superior vena cava if the injection is accomplished from above, or a diminution of the inferior vena cava if the injection is from the femoral

vein. The elevated venous pressures cause reflux into these vessels. The increased intrathoracic pressure also is at least partly responsible for closure of the tricuspid valve with consequent enhanced opacification of the right atrium. Right ventricular and pulmonary artery opacification is diminished, the latter associated with some increase in caliber, but less density.

The authors ascribe most of the above changes to the slowing of flow in the extrathoracic veins toward the thorax, and to the temporary arrest of flow in the intrathoracic veins and in the right atrium.

SCHWEDEL

Shumway, N. E., and Lewis, F. J.: The Closure of Experimental Aortic Septal Defects under Direct Vision and Hypothermia. Surgery **39:** 604 (Apr.), 1956.

An experimental study was performed on dogs in whom a shunt was made between the aorta and pulmonary artery; later the defect was closed under direct vision with hypothermia.

The authors concluded that aortic septal defects could be easily repaired under direct vision and hypothermia through the pulmonary artery.

ABRAMSON

Lillehei, C. W., Winchell, P., Adams, P., Baronofsky, I., Adams, F., and Varco, R. L.: Pulmonary Valvular Stenosis with Intact Ventricular Septum. Results of the Brock Type Valvulotomy. Am. J. Med. **20:** 756 (May), 1956.

In 20 patients studied before and after the Brock valvulotomy, the average preoperative right ventricular systolic pressure was 116 mm. Hg, the average postoperative value 56 mm. Hg. Excluding 5 cases in which no significant change occurred, the average preoperative value was 123 and the postoperative value 43 mm. Hg. The 5 failures may be ascribed to undetected infundibular pulmonary stenosis or to the possibility that the valvulotome slipped through a fibrous valve without making an incision. In a group of 7 patients with right-to-left shunt at the atrial level, the average preoperative right ventricular systolic pressure was 143 mm. Hg and the postoperative 45 mm. Hg. In addition the hemoglobin dropped from 20.0 to 15.3 Gm. per cent and the arterial oxygen saturation rose from 75 to 89 per cent. Vigorous dilatation of the valve following incision with the valvulotome is deemed an important determinant of a successful operation.

HARRIS

UNCOMMON FORMS OF HEART DISEASE

Blattner, R. J.: Cardiac Involvement in Certain Virus Diseases. J. Pediat. **49:** 234 (Aug.), 1956.

Involvement of the myocardium in virus diseases has been reported recently in 2 widely published articles. Four cases of myocarditis in children with hepatitis were described by Saphir at the Michael Reese Hospital. No cultural studies on autopsy material were obtained to prove that the infection in the myocardium was viral in origin. In Johannesburg, South Africa, during an outbreak of Coxsackie group B virus infection in a maternity hospital, 10 infants, of whom 6 died, developed myocarditis. Suggestive bacteriologic confirmation was obtained in 2 cases that this was truly a viral myocarditis although the evidence is not definitive. (This report which appeared in the J. Pediat. for Jan. 1956, has been reviewed in these columns by the reviewer.) Dr. Blattner in his comment on current literature calls attention to these 2 reports and stresses the importance of further investigation to prove "viral myocarditis."

HARVEY

Duque Sampayo, A., and Perez Gonzalez, P.: Sclerodermic Heart Disease. Rev. españ. cardiol. **9:** 417 (Dec.), 1955.

A 25-year-old woman with scleroderma and Raynaud's disease showed mild dyspnea, enlargement of both ventricles and atria in the x-ray and low-voltage with ventricular extrasystoles in the electrocardiogram. The blood pressure was 110/75. This is the first case presented in Spain.

LEPESCHKIN

Guraieb, S. R., and Rigdon, R. H.: Fibroelastosis in Adults. A Review of the Literature and Report of a Case. Am. Heart J. **52:** 138 (July), 1956.

Twenty-four cases of fibroelastosis in adults reported from America and England are summarized in table form with relation to age, sex, heart weight, blood pressure, murmurs, and electrocardiographic findings. Another case in a 38-year-old white man is reported. The author believes that the process in the adult is congenital in origin. The pathologic lesions in the heart of the adult are identical with those observed in infants. The histologic findings are the presence of elastic tissue and a thin band of cardiac muscle in a thickened endocardium in the absence of any inflammatory reaction.

RINZLER

Bernreiter, M.: Unusual Electrocardiographic Findings in Cardiac Amyloidosis. J.A.M.A. **161:** 441 (June 2), 1956.

In this case of severe cardiac amyloidosis the usual electrocardiographic findings of low QRS and T-wave voltage in the extremity leads plus changes in the precordial leads suggestive of myocardial scarring were noted. There was also electric alternation of the P waves, which had not previously been reported in such cases.

KITCHELL

Bender, F. and Hegemann, F.: Clinical Observations in Traumatic Rupture of the Ventricular Septum. Ztschr. Kreislaufforsch. **45:** 352 (May), 1956.

A 22-year-old male suffered precordial trauma by the steering wheel in an automobile accident, followed by the appearance of an intense systolic murmur and signs of congestive heart failure. The electrocardiogram showed wide Q, elevated S-T and inverted T in lead I. After 4 months' cardiac catheterization was carried out, during which the catheter entered the left ventricle, the pressure there was 98/12 while in the right ventricle it was 46/2. The calculated left-to-right shunt was 5.6 L. per min. Three months later the right ventricular pressure was still 35/3 but signs of heart failure had disappeared and the patient could play football and swim without any complaints.

LEPESCHKIN

Thomas, W. A., Lee, K. T., McGavran, M. H., and Rabin, E. R.: Endocardial Fibroelastosis in Infants Associated with Thrombosis and Calcification of Arteries and Myocardial Infarcts. New England J. Med. **255:** 464 (Sept. 6), 1956.

The material from 2 infants with calcific arterial disease and myocardial infarction was reviewed together with that of 24 infants dying with uncomplicated endocardial fibroelastosis with valvular involvement, 2 infants with a left coronary artery arising from the pulmonary artery and associated myocardial infarcts, 1 infant with endocardial fibrosis, mural thrombosis and myocardial infarction with calcified arterial lesions and 5 rabbits with myocardial infarction resulting from embolization with blood clots. The association of calcific arterial disease in infants with endocardial fibroelastosis is said not to have been reported previously and since both diseases are so uncommon it is believed that their co-existence in the 2 cases reported here is more than fortuitous. Several possible correlations of the 2 diseases are discussed. The authors are of the belief that the most probable is that the endocardial fibrosis was the underlying disorder and that the arterial disease and myocardial infarction resulted from emboli originating from mural thrombi attached to the endocardium.

ROSENBAUM

Kubát, K. and Todorovičová, H.: Contribution to the Problem of Mesotheliomatas of the Pericardium. Cardiologia **29:** 385 (No. 6), 1956.

Clinical, anatomic and histologic findings are described in a 61-year-old woman with a malignant primary tumor of the pericardium. The clinical manifestations were dominated by progressive congestive heart failure. Anatomically, the origin of the tumor could be located to the basal portion of the visceral pericardium spreading from there into the myocardium as well as to the parietal pericardium and resulting in obliteration of the pericardial cavity and constriction of the heart. Histologically the tumor corresponded to a mesothelioma. Views of various authors concerning the histogenesis and the morphologic entity of mesotheliomatas are reviewed.

PICK

Hull, H., Kissane, R. W., and Fidler, R. S.: Myolypoma of the Heart. A Case Report. Exper. Med. & Surg. **13:** 300, 1955.

A review of the literature indicates that there have been only 33 reported cases of primary lipoma of the heart. A case is reported of primary endocardial lipoma situated in the right atrium of a 67-year-old white male. The tumor was subendocardial, did not have a well-defined capsule, had strands of compressed myocardium or muscle cells passing through the adipose tissue and was well demarcated at the periphery from the rest of the myocardium. Fatty infiltration was not found elsewhere in the myocardium. It was proposed that these tumors be classified into lipoma, fibrolipoma, and myolipoma; the tumor in this report was classified as a myolipoma.

MAXWELL

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

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AHA ANNUAL MEETING AND SCIENTIFIC SESSIONS

The special Scientific Session for Physicians in General Medicine, on Friday, October 25, which precedes the Association's regular Scientific Sessions in Chicago, October 26–28, has been classified by the American Academy of General Practice as acceptable for Category II credit for Academy members.

This all-day teaching program for general practitioners, under the chairmanship of Howard B. Sprague, M.D., Boston, will include, during the morning hours, presentations on "Prevention and Management of Cardiovascular Emergencies" in pregnancy, in children, during anesthesia, after surgery, during drug therapy and in anxiety states. These will be followed by an afternoon discussion period and a panel on "Unsettled Questions in the Management of Cardiovascular Disease." Louis N. Katz, M.D., Chicago, will be panel moderator. Scheduled for Friday evening is another special session, "Instrumental Methods of Cardiovascular Diagnosis" under the chairmanship of Charles E. Kossmann, M.D., New York. All events will take place as part of the Association's Annual Meeting at the Hotel Sherman.

The following is the program of the regular Scientific Sessions as well as highlights of the Annual Meeting program:

Saturday morning, October 26: The Scientific Sessions will be opened by the Association's President, Edgar V. Allen, M.D., Rochester, Minnesota. Dr. Allen's remarks will honor William Harvey whose death 300 years ago will be commemorated by the series. He will then present special citations to Nobel Prize laureates, Drs. André F. Cournand and Dickinson W. Richards, Jr., of New York. The General Session (Chairman: Dr. Allen; Co-Chairman: George E. Burch, M.D., New Orleans) will feature the Lewis A. Conner Memorial Lecture by Charles Rammelkamp, M.D., Cleveland. The Association's Council on Rheumatic Fever and Congenital Heart Disease will hold its annual luncheon. *Afternoon:* Simultaneous Scientific Sessions of the Council on Clinical Cardiology (*Chairman: William P. Thompson, M.D., Los Angeles; Co-Chairman: Wright R. Adams, M.D., Chicago*), Council on Circulation (*Chairman: Herbert Chasis, M.D., New York; Co-Chairman: Milton Mendlowitz, M.D., New York*), Council on Rheumatic Fever and Congenital Heart Disease (*Chairman: Maclyn McCarty, M.D., New York; Co-Chairman: Jesse E. Edwards, M.D., Rochester, Minn.*) and the Council on Basic Science (*Chairman: Eric Ogden, M.D., Columbus, Ohio; Co-Chairman: James W. McCubbin, M.D., Cleveland*).

Sunday morning, October 27: General Session, (*Chairman: Irvine H. Page, M.D., Cleveland; Co-Chairman: Edgar A. Hines, M.D., Rochester, Minn.*), including the George E. Brown Memorial Lecture by Nelson W. Barker, M.D., Rochester, Minn., on "Current Evaluation of the Thrombosis Problem." The Community Service and Education Council will hold its annual luncheon. *Afternoon:* General Sessions (*Chairman: Robert W. Wilkins, M.D., Boston; Co-Chairman: Harold Feil, M.D., Cleveland*). Joint program of the Community Service and Education Council and the Staff Conference of Heart Associations on "Community Service—Its Nature and Its Significance for Heart Associations." In addition, the Council will sponsor, as part of the Scientific Sessions, a panel moderated by Herbert Pollack, M.D., Chairman, of the Association's Nutrition Committee, on "Lipid Metabolism and Arteriosclerosis." The Albert Lasker Award of the American Heart Association will be presented by Dr. Wilkins, President-Elect of the Association. *Evening:* Annual Dinner of the Association including the presentation of Gold Heart Awards.

Monday morning, October 28: Simultaneous Scientific Sessions of the Council on Cardiovascular Surgery (*Chairman: Frank Glenn, M.D., New York; Co-Chairman: John H.*

Gibbon, Jr., M.D., Philadelphia) and the Council for High Blood Pressure Research (*Chairman: Meyer Friedman, M.D., San Francisco*).

Six Assembly Panels will be in session on Monday. They will discuss the following subjects:

Research (Chairman: Eugene A. Stead, Jr., M.D., Durham, N. C.; Co-Chairman: Harold Green, M.D., Winston-Salem, N. C.).

Fund Raising and Public Relations (Chairman: Stenson White, Cleveland; Co-Chairman: Wendell B. Gordon, M.D., Pittsburgh and John D. Brundage, Montclair, N. J.).

Relationships and Responsibilities Between National, State and Local Heart Associations (Chairman: Harry B. Weinberg, M.D., Davenport, Iowa: Co-Chairman: Merrit H. Stiles, Spokane).

Community Service (Chairman: Frederick G. Gillick, M.D., Omaha; Co-Chairman: Thomas L. Ross, Jr., Macon, Georgia).

Heart Association Support of Medical Schools (Chairman: E. Cowles Andrus, M.D., Baltimore; Co-Chairman: Edgar Hull, M.D., New Orleans).

Heart Association Services to Professional Groups (Chairman: Wright R. Adams, M.D., Chicago; Co-Chairman: Currier McEwen, M.D., New York).

Tuesday morning, October 29: Annual Session of the Associations general Assembly, which will review panel recommendations and elect officers and Board members of the Association.

AHA GRANT APPLICATIONS DUE BY NOVEMBER 1

Applications for Heart Association grants-in-aid during the fiscal year beginning July 1, 1958 must be received by the National Office no later than November 1, 1957. The deadline for submitting applications for Research Fellowships and Established Investigatorships was September 15.

All applications must be made on forms available from the Association's Assistant Medical Director for Research. Grants are made to non-profit institutions in direct support of a particular investigator, for a specific program of research under his direction. Grants are awarded in support of research in the cardiovascular field or basic sciences related to it for periods of one to five years.

CATALOGUE OF PROFESSIONAL MATERIALS AVAILABLE FROM ASSOCIATION

A revised, comprehensive catalogue, "Publications and Teaching Aids for Physicians," listing all professional materials of the American Heart Association, is available from the National Office of the AHA or local Heart Associations. The catalogue includes prices, a brief description of each item, a foreword and an index.

ASSOCIATION ISSUES VARICOSE VEINS BOOKLET

"Varicose Veins" is the title of a new illustrated booklet published by the American Heart Association for distribution by physicians to their patients. The publication tells what varicose veins are, and how they develop. It points out danger signs, emphasizes the need for periodic checking with physicians, describes types of treatment and concludes with "What Doctors Advise," a list of helpful suggestions.

Single copies of the booklet are available free of charge from the American Heart Association and local Heart Associations.

ALFRED M. BENNETT, M.D., JOINS NATIONAL MEDICAL STAFF

Alfred M. Bennett, M.D., has joined the Medical Division of the Association's National Office as Medical Associate in the area of Rheumatic Fever and Congenital Heart Disease.

Dr. Bennett's new duties will involve staff work with the Association's Council on Rheumatic Fever and Congenital Heart Disease. He will also be responsible for advising on rheumatic fever prevention programs conducted by the affiliates and chapters of the American Heart Association.

Dr. Bennett previously served as Associate in Medicine, Department of Medicine, Emory University Medical School, Atlanta. He received his medical degree at the University of

Illinois in 1947 and later carried out studies of liver disease during a 2-year fellowship at the Department of Medicine, Northwestern University. His writings include medical papers on the epidemiology of infectious hepatitis in children.

PUBLISHER HONORED

Henry M. Stratton, President of Grune & Stratton, Inc., publishers of Circulation and Circulation Research, was awarded an honorary degree of Doctor of Medicine by the University of Freiburg, Germany, last June. He is the first layman from the United States to receive such an award from this University.

MEETINGS CALENDAR

October 1–4: American Roentgen Ray Society, Washington, D. C. Barton R. Young, Germantown Hospital, Philadelphia 44, Pa.

October 7–10: American Academy of Pediatrics, Chicago, Ill. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill.

October 14–18: American College of Surgeons, Atlantic City, N. J. Michael L. Mason, 40 E. Erie St., Chicago 11, Ill.

October 14–19: American Society of Anesthesiologists, Los Angeles, Calif. J. E. Remlinger, Jr., 188 W. Randolph St., Chicago 1, Ill.

October 18–21: Third International Congress of the International Society of Angiology, Ambassador Hotel, Atlantic City, N. J. Dr. Henry Haimovici, 105 E. 90th St., New York 28, N. Y.

October 21–23: Association of American Medical Colleges, Atlantic City, N. J. Dean F. Smiley, 2530 Ridge Ave., Evanston, Ill.

October 22–25: American Dietetic Association, Miami, Fla. Mrs. Thelma Pollen, 620 North Michigan Ave., Chicago 11, Ill.

October 23–25: American Association of Medical Clinics, Kansas City, Mo. Harold D. Caylor, Caylor-Nickel Clinic, Bluffton, Ind.

October 25–28: Scientific Sessions of the American Heart Association, Chicago, Ill. American Heart Association, 44 East 23rd St., New York 10, N. Y.

November 1–9: School Health Association, Washington, D. C. M. F. Shanholtz, M.D., State Office Bldg., Richmond, Va.

November 3–4: American Society for the Study of Arteriosclerosis, Chicago, Ill. O. J. Pollak, M.D., P.O. Box #228, Dover, Del.

November 11–15: American Public Health Association, Cleveland, Ohio. R. M. Atwater, M.D., 1790 Broadway, New York 19, N. Y.

November 17–22: Radiological Society of North America, Chicago, Ill. D. S. Childs, M.D., 713 E. Genesee St., Syracuse 2, N. Y.

November 22–23: Council for High Blood Pressure Research of the American Heart Association, Cleveland, Ohio. Mrs. Jerry H. Bruner, 1689 East 115th St., Cleveland 6, Ohio.

December 3–6: American Medical Association, Philadelphia, George F. Lull, 535 N. Dearborn St., Chicago 10, Ill.

ABROAD

September 29–October 5: World Medical Association, Istanbul, Turkey. Louis H. Bauer, M.D., 10 Columbus Circle, New York 19, N. Y.

October 27–November 2: Congress of International Society of Surgery, Mexico City, Mexico. Dr. L. Dejardin, 141, Rue Belliard, Brussels, Belgium.

September 14–21, 1958: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

PROGRAM AND PROCEEDINGS OF THE ELEVENTH ANNUAL MEETING AT THE KNICKERBOCKER HOTEL, CHICAGO, ILLINOIS, NOVEMBER 2, 3 AND 4, 1957

(All papers except the Addresses will be limited to 10 minutes for presentation plus 5 minutes for discussion.)

SATURDAY AFTERNOON NOVEMBER 2, 1957

J. C. Paterson, Presiding

1:00 Registration

2:00

1. Relation of Oil Composition to Serum Cholesterol Levels in Hypercholesterolemic Rats

D. M. Hegsted, Anna Gotsis and F. J. Stare. From the Department of Nutrition, Harvard School of Public Health, Boston, Mass.

The hypercholesterolemia produced by feeding cholesterol and cholic acid to rats is influenced by the kind of fat fed. This has been used as an assay to study the effect of different oils and combinations of oils upon serum cholesterol levels. At the time the abstract was written, 65 different oils or combinations of oils have been investigated.

The highest serum cholesterol levels were obtained with tung oil, olive oil, and a "triolein preparation" containing 88 per cent oleic acid. The addition of many other oils to the "triolein" preparation or tung oil decreased the serum cholesterol levels.

Various ways were tried to account for the activity of the different materials tested. It is clear that the linoleic acid content alone does not account for the cholesterol lowering effect. However, an excellent inverse relationship was found between the serum total cholesterol level and the product obtained by multiplying the saturated acid content of the diet by the linoleic acid content. In a series of 24 oil combinations studied at 1 time (6 animals per group) a straight line relationship between the product and serum cholesterol was found upon a log-log plot with a correlation coefficient of $-.94$.

Thus it appears that under these conditions hypercholesterolemia is promoted by nonessential unsaturated fatty acids and that this action is counteracted by a synergism between the saturated and essential fatty acids. In order to make linseed oil "fit" the curve, linolenic acid had to be considered nonessential. Limited data indicate that arachidonic acid has an action like linoleic. The activity of coconut oil, lard, palmitic acid and pelargonic acid, etc., when added to "triolein" indicates no effect of chain length upon activity of the saturated acids. Maximum cholesterol lowering was obtained when the fat of the diet was 50 per cent coconut oil and 50 per cent safflower oil.

2:10

2. Effects of Ethyl Linoleate, Ethyl Oleate, Trilinolein, Triolein, and of a Phosphatide Mixture Containing Tetranoic Acid, upon Fatty Acid Composition of Plasma Lipids in Normal and Abnormal Subjects

Laurance W. Kinsell, George D. Michaels and J. P. Dailey. From the Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, Calif.

Recent work has shown that the addition of highly purified poly-unsaturated fatty acid preparations to quantitatively constant diets is associated with a major decrease in plasma cholesterol and usually a lesser fall in plasma phospholipid. The mechanism of this effect requires clarification.

In the present study, 1 young normal male subject, and patients with familial hypercholesterolemia and with other forms of congenital and acquired disturbances of lipid metabolism have been evaluated on the metabolic ward from the standpoint of plasma lipid changes during the administration of ethyl linoleate (96 per cent pure), ethyl oleate, trilinolein, triolein, and a phosphatide of animal origin containing approximately 12.5 per cent of a tetranoic acid (probably the biologically-natural form of arachidonic acid). All of these preparations except the ethyl oleate and triolein have produced a highly significant and maintained fall in plasma cholesterol. In 1 young male with familial hypercholesterolemia huge amounts of ethyl linoleate were required to produce this effect.

In an approach to mechanism of action, cholesterol esters have been quantitatively isolated by

column fractionation, and net changes in fatty acid composition determined. The same statement applies to the total plasma phospholipids, and by difference to the plasma neutral fat. Without exception, the administration of purified poly-unsaturated material to date has resulted in a maintained net increase in the essential fatty acids esterified with cholesterol. Changes in phospholipid fatty acid composition have not been interpretable. It is anticipated that fractionation of the phospholipids will provide more meaningful data.

2:20

3. Serum Cholesterol Response to Natural and Hydrogenated Fats

Ancel Keys, Joseph T. Anderson and Francisco Grande. From the Laboratory of Physiological Hygiene of the University of Minnesota and the Hastings State Hospital, Minn.

Groups of 12 to 27 men were maintained on a series of diets differing only in kind or amount of fat which was isocalorically exchanged for carbohydrate. Nine series of experiments provided 58 sets of dietary comparisons and corresponding cholesterol responses. It was postulated that other things being equal the cholesterol response may be the resultant of changes of saturated (S), monoethenoid (M) and polyethenoid (P) fatty acids in the diet, where these are expressed as per cent of total diet calories: Δ Chol. $= b\Delta S + c\Delta M + d\Delta P$.

The experimental data indicated no significant effect of ΔM and yielded $b = 2.74$ and $d = -1.31$ for the least-squares solution for 41 comparisons involving butterfat, lard, olive oil, cottonseed oil, sunflower seed oil, and mixed fats in ordinary American diets at levels of 9 to 42 per cent fat calories. These coefficients predicted accurately average results in 4 sardine oil comparisons but slightly overestimated cholesterol values in 15 comparisons involving 100 Gm. corn oil daily; cholesterol values on corn oil were somewhat low. Agreement with the equation was satisfactory in 3 experiments with butter and margarine feeding of Japanese coal miners, in 2 experiments on mental patients fed 30 and 100 Gm. daily of safflower oil and in an experiment on 141 students fed butterfat, olive oil or safflower oil but cholesterol values on corn oil were slightly low. For all the natural fats tested, data on cholesterol responses indicate that roughly 1 Gm. of saturated fat offsets the effect of 2 Gm. of linoleic acid, that oleic acid has very little effect, and that the magnitude of the response is related to the duration of the diet change and to the intrinsic cholesterol level of the individual.

In 2 experiments comparing natural with hydrogenated safflower oil and in an experiment comparing natural with hydrogenated corn oil the effects of hydrogenation were less than predicted by the equation; hydrogenation did not lead to cholesterol values as high as predicted from ΔS and ΔP.

2:30 Discussion

2:45

4. Further Observations on Normal and Atherosclerotic Aortic Homotransplants in Anterior Eye Chambers of Rabbits

A. C. Higginbotham. From the Department of Anatomy, School of Medicine, West Virginia University, Morgantown, W. Va.

Homotransplants of normal and atherosclerotic aortas were made into anterior eye chambers of rabbits according to the method recently described by the author (Science **125:** 554, 1957). Gross study of the transplants in situ and histologic and histochemical studies were made on transplants removed from treated and untreated hosts at intervals over several months.

Transplantation of atherosclerosed artery into the anterior eye chambers of healthy host animals by this method immediately minimizes factors favoring atherogenesis, thus providing lesions more sensitive to pharmacologic agents and diets than those within animals in which they were developed by rigorous atherogenic procedures. Also, since the atherogenic processes are minimized, identification and study of the sequential changes occurring during regression of lesions of known features can be done with a greater degree of certainty.

The transplants of normal and atherosclerosed aorta persisted for several months in treated and untreated hosts. Vascularization of the adventitia of both types of transplants by blood vessels from the iris occurred within 8 days. Extensive vascularization of atherosclerotic intima occurred within 30 days, but vascularization of normal intima has not been observed.

The regressive changes which occurred in plaques of transplants of atherosclerotic aorta in untreated healthy host animals were described at the meetings of the American Association of Anatomists (Anat. Rec. **127:** 308, 1957). These changes included a reduction in the number of foam cells and their replacement by collagenous tissue, the conversion of cholesterol esters to cholesterol crystals with formation of clefts between the cells, and a decrease in material stainable with oil red O.

Preliminary observations suggest that the regressive changes seen in the atherosclerotic transplants in untreated hosts may be modified by certain pharmacologic agents and diets in hosts receiving these agents and diets.

These studies are in progress and the results will be reported.

2:55 Discussion

3:00

5. Effect of Dietary Fat on Serum Cholesterol Levels in Infancy and Childhood

Julius Pomeranze, Alta Goalwin and Lawrence B. Slobody. From the Departments of Medicine and Pediatrics, New York Medical College, Metropolitan Medical Center, N. Y.

Serum cholesterol levels can be lowered when the proportion of fat in the diet is substantially reduced. In contrast to this, if the fat is of vegetable origin, serum cholesterol levels may be depressed even in the presence of increased dietary fat. Although the evidence that serum cholesterol levels are a measure of an atherogenic tendency is far from satisfactory, the probability of such a relationship cannot be ignored.

Since atherosclerosis has its inception in infancy and early childhood and is probably reversible during the first 15 years of life (Holman, AMA meeting Fat Metabolism, March 1957; Pomeranze, Lancet, July 7, 1956), the relationship of dietary fat, hypercholesterolemia and atherogenesis in these early years requires further study. As a preliminary experiment serum cholesterol levels were determined at birth and at weekly intervals for the first year of life in infants fed either an evaporated milk formula or a commercial soy milk formula. Subsequently these studies were extended to include infants to whose evaporated milk formula 50 Gm. of corn oil was intermittently added and removed.

Serum cholesterol levels at birth and within the first few days of life range from 60 to 80 mg per cent. In infants on an evaporated milk formula these rise rapidly during the first four months of life to 140 to 180 mg per cent. This is in sharp contrast to the minimal rise in serum cholesterol of infants fed a soy milk formula. Infant serum cholesterol levels reported from Italy differ markedly from those of infants fed an evaporated milk formula and are similar to those of infants fed a soy milk formula.

When 50 Gm. of corn oil was added to the evaporated milk formula serum cholesterol levels dropped significantly. When the lowered level was maintained for a few weeks, corn oil was removed from the formula feeding. Serum cholesterol levels promptly rose. This has been repeated a number of times and the results have been consistent.

The significance of these findings must await further elaboration both of the effect of unsaturated fats on serum cholesterol levels and of the relationship of serum cholesterol to atherogenesis in childhood and adult life.

3:10 **Discussion**

3:15

6. Human Plasma Heparin Levels Following Intravenous Fat Emulsions

Hyman Engelberg. From Beverly Hills, Calif.

Circulating heparin(s) levels were determined before, during and after the administration of intravenous fat emulsion (Lipomul) for 1 hour. The method used for the extraction and separation of endogenous circulating heparin was a modification of the technic suggested by Nillson and Wenckert in which heparin is first adsorbed on tricalcium phosphate gel, then eluted with citrate, and the octylamine brucine method of Jacques applied to the eluate. The end product was reversible by protamine, and was assayed by metachromatic and anticoagulant technics using standard curves obtained with commercial heparin. It is probable that chondroitin sulphate is also present in the final extract, but it has no or only trace anticoagulant activity.

There was increased metachromatic activity in 5 of the first 6 patients studied, and parallel increases in anticoagulant titer although not always to the same degree. The rise in heparin titer did not occur in the first 15 minutes after the intravenous fat was started but was found after 1 hour. In several cases the elevated level was present 1 hour after the intravenous was discontinued; in others it had fallen to control values. In 1 patient the heparin titer fell during the fat drip.

Studies in a larger series will be presented. The initial results indicate that a fairly marked increase in endogenous circulating heparin levels occurs following the intravenous administration of fat.

3:25 **Discussion**

3:30

7. Production of Coronary Thromboses and Myocardial Infarcts in Rats by Dietary Means

W. Stanley Hartroft and Wilbur A. Thomas. From the Department of Pathology, Washington University Medical School, St. Louis, Mo.

Seven groups, each consisting of 10 male Wistar rats (initial weights 110 Gm.) were fed a basal diet containing 0.3 per cent thiouracil, 2 per cent sodium cholate and 5 per cent cholesterol. The protein content ranged from 20 per cent (casein) to 12 per cent (equal parts casein and alpha soya protein). Dietary fat fed to 3 of the groups (20 per cent casein) consisted of 10 per cent corn oil with a choline chloride supplement of 0, 0.2 or 1.0 per cent respectively. In one group (20 per cent casein), the fat level was raised to 40 per cent (equal parts corn oil and Crisco) at the expense of the carbohydrate. Another group received butter (40 per cent) in the 20 per cent casein diet. Two final groups (6 per cent casein and 6 per cent alpha soya protein) received 40 per cent lard, and 1 of these groups was given a supplement of 1 per cent choline chloride (mortality from hemorrhagic renal lesions in this choline-deficient group was high, 7 of 10) during the first month of the experiment which lasted 14 weeks. During the last 2 months of the experiment, examination of

several of the animals which died revealed gross and microscopic evidence of coronary thromboses and myocardial infarcts. The greatest numbers of cardiac infarcts occurred in the groups fed 40 per cent butter or 40 per cent lard (with choline supplements). Renal infarcts were also encountered. The results will be presented with the aid of tables and photomicrographs.

3:40

8. Pathologic Findings in Sudden and Unexpected Death from Occlusive Coronary Artery Disease

Milton Helpern and Sidney B. Weinberg. From the Medical Examiner's Office, Bellevue Hospital, New York, N. Y.

The most common cause of sudden and unexpected natural death is occlusive coronary arteriosclerosis. Autopsy studies in the Office of the Chief Medical Examiner, New York City, indicate that approximately 50 per cent of all sudden natural deaths result from heart disease. Of these, two-thirds are primarily caused by occlusive disease of the coronary arteries. Prior and present studies demonstrate that in about 70 per cent of such unexpected deaths, many are without previous history of disability or knowledge of pre-existing disease. The occlusive process is a result of gradually progressive coronary atherosclerosis. Some of these cases reveal evidence of old acute thrombotic lesions, the precise character of which were difficult to evaluate with respect to their relationship to hemorrhage within atheromatous plaques. In about one half of these cases, there is evidence of myocardial fibrosis of varying extent indicative of episodes of previous frank myocardial infarction or of irreversible myocardial damage associated with coronary insufficiency.

In about 30 per cent of fatalities from occlusive coronary artery disease, acute occlusive lesions were found as complications of the sclerotic process.

The present report is concerned with a detailed study by use of serial section technique of these acute occlusive lesions. In this study approximately 80 per cent of the thrombotic lesions of the coronary arteries were found associated with significant intimal hemorrhages.

3:50 Discussion

4:00

9. Surfactant Effects on Plasma Gels

Herbert L. Davis and Nora L. Davis. From the Departments of Biochemistry and Surgery of the University of Nebraska College of Medicine, Omaha, Neb.

Gel times obtained by the recalcification of human citrated plasmas provide qualitative and quantitative comparisons of added clinically effective antihemorrhagic and antithrombotic materials. Most of these fall into 1 of 4 classes with regard to their modification of the charge and/or the hydration of fibrinogen. Blood proteins depend on charge and hydration for their dispersion stability, and lowering either or both of these stability factors to some intermediate state results in gel formation. Excess of effective coagulant agents then inhibits gel formation, and finally produces precipitation.

Coagulant agents are cationic substances (protamine, toluidine, polybrene) which reduce the negative charge, or they are surfactant materials (alcohols, lipids, soaps) which reduce the hydration of the proteins. Anticoagulants are anionic agents (heparin, heparinoids) to increase the charge, or they are strongly hydrated substances (albumin, dextran) which increase the hydration stability. Plasmas treated with these reagents and then recalcified give gel times and antagonistic effects generally correlated with their demonstrated clinical properties.

Notable is the effect of lipids and soaps in showing marked coagulant effects in vitro. These may be correlated with the increased coagulability of whole blood after a meal rich in lipids, with the increased coronary death rates in populations on diets high in fats, and with the general colloidal stability of the blood sol in conditions of natural balance. Notable also is the much greater coagulant effects of saturated fatty acid soaps (stearate) than the unsaturated ones (oleate). Many citrated plasmas form firm gels in a few minutes on addition of sodium stearate alone. This suggests a mechanism of blood clotting by surfactants and lipids, and independent of calcium ions. Many coagulant agents reduce gel times at low concentrations, and then retard or prevent gel formation at higher concentrations.

4:10 Discussion

4:15

10. Lipids, Lipoproteins and Diet in Clinical Coronary Atherosclerosis

J. A. Little and H. M. Shanoff. From the Department of Veterans' Affairs, Sunnybrook Hospital, Toronto, Ontario, Canada.

Although it is now accepted that serum lipid-lipoprotein abnormalities do occur in human atherosclerosis, the relative importance of the different fractions has been controversial. Accordingly, serum cholesterol (total, free and ester), phospholipids, C/P ratio and standard S_f 0–12, 12–20, 20–100, 100–400, 0–400 and 12–400 were determined in a group of 116 males with clinical coronary atherosclerotic heart disease and in a matched control group age 30 to 80. Both groups were carefully selected so as to be free of hypertension, secondary hypercholesterolemic states or other complicating diseases.

All the lipid fractions did not vary with age in the control group. All were significantly elevated in the coronary group up to age 60.

The relative ability of the different lipid fractions to distinguish between the coronary and control groups was assessed. Total, ester and free cholesterol, C/P ratio, standard S_f 0–12 and 0–400 lipoproteins were superior to the other fractions and approximately equal to each other. At best their distinguishing ability had a 20–40 per cent error. The determination of total serum cholesterol remains the simplest laboratory test showing significant correlation with coronary atherosclerosis but is far from diagnostic in the individual.

Dietary studies showed no important difference in total calories or total fat between the control and coronary groups. Clearly, other factors must account for the higher serum lipids in the coronary group.

4:25 Discussion

4:30

11. Effects of Oleic Acid on Plasma Lipids and Atherogenesis in Cholesterol-Fed Cockerels

Jeremiah Stamler, Ruth Pick and Louis N. Katz. From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

This experiment was undertaken to study the effects of a mono-unsaturated fatty acid on plasma lipids and atherogenesis in cholesterol-fed chicks. Two groups of cockerels were observed during the age period 14–19 weeks: (1) control, mash + 1 per cent cholesterol + 10 per cent cottonseed oil; (2) experimental, mash + 1 per cent cholesterol + 10 per cent oleic acid. The experimental group had significantly greater hypercholesterolemia, and hepatic and visceral lipidosis. In contrast, incidence of aorta atherogenesis was reduced in the oleic acid fed chicks. Further studies are in order to clarify the mechanism and significance of this apparent dissociation of lipid metabolic and atherogenic effects.

4:40 Discussion

4:45

12. Development of Atherosclerosis in the Major Cerebral Arteries

James C. Roberts, Jr. and Campbell Moses. From the Department of Pathology and the Addison H. Gibson Laboratory of the University of Pittsburgh School of Medicine, Pittsburgh, Pa.

Detailed morphologic studies of all the accessible arteries in over 400 consecutive adult autopsies in a general hospital have been made. All gross lesions have been graded as to extent and severity. Over 300 of these examinations (75 per cent) have included study of the 12 major cerebral vessels in patients of various ages dying from various causes, usually not central nervous system disease. Atherosclerotic profiles of the various age and disease groups are presented and the development of cerebral atherosclerosis discussed. Emphasis is placed on the sporadic and infrequent occurrence of atherosclerosis of the major cerebral arteries in general hospital patients without clinical signs of cerebrovascular disease.

4:55 Discussion

SUNDAY MORNING

Charles F. Wilkinson, Jr., Presiding

8:00 Registration

9:00

13. The Arterial Wall as an Organ

Russell L. Holman, Henry C. McGill, Jr., Jack P. Strong and Jack C. Geer. From the Department of Pathology, Louisiana State Univeristy School of Medicine, New Orleans, La.

Studies following gross staining with sudan IV of 1250 aortas, age 1 to 40 years, obtained from 8 geographic areas (New Orleans, England, Spain, South Africa, Guatemala, Costa Rica, Puerto Rico and Colombia) have revealed that practically every case beyond the age of 3 years—regardless of sex, race, blood pressure, blood lipid levels, nutritional status or principal cause of death—has shown at least some degree of intimal sudanophilia. Histologic and histochemical studies of several grossly negative aortas less than 3 years of age have shown occasional intracellular deposits of lipid without extracellular lipid. The reverse—extracellular lipid without intracellular lipid—has not been observed. Abundant evidence from other sources as well as our intensive studies of the early stages of human atherosclerosis have emphasized the importance of the arterial wall as an organ capable of synthesizing, accumulating and removing lipids as well as carrying on other metabolic functions in response to local and, especially, to systemic (hormonal) factors.

9:10

14. Aortic Synthesis of Plaque Phospholipids in the Eviscerated Nephrectomized Cholesterol-Fed Rabbit

E. L. McCandless and D. B. Zilversmit. From the Department of Physiology, University of Tennessee, Memphis, Tenn.

Phospholipid concentrations increase in aorta and plasma of cholesterol-fed rabbits. Plasma increments are almost maximal after 1 month on a 1 per cent cholesterol diet, at which time aortic concentrations are only slightly elevated. Aortic concentrations increase to a maximum of 400 per cent after 3 months on the diet, in the presence of continuing

hyperphospholipemia. This sequence of events has prompted the assumption that aortic phospholipids originated from the plasma phospholipid pool. However, our own studies have shown that the excess aortic phospholipids are derived by aortic synthesis rather than by deposition from plasma (Arch. Biochem. & Biophys. **62:** 402, 1956). This conclusion was confirmed by a study of P^{32} incorporation into aortic phospholipids in eviscerated nephrectomized rabbits, in which plasma phospholipid synthesis is minimal. In cholesterol-fed rabbits, 4 hours after P^{32} administration specific activities of phospholipids of the whole atheromatous aortic intima were 2.5 to 6.0, while the plasma phospholipid specific activities were 0.02 to 0.28. Although plasma specific activities were decreased to 1 to 8 per cent of normal, the incorporation of P^{32} into aortic phospholipids was unaffected by evisceration. The fact that aortic phospholipid specific activities were 30 to 100 times greater than plasma specific activities provides strong evidence against the derivation of even a small fraction of aortic phospholipid by deposition from plasma.

9:20

15. Response of the Aorta In Vitro to Hormones and a Vitamin

N. T. Werthessen. From the Department of Physiology and Biochemistry, Southwest Foundation for Research and Education, San Antonio, Tex.

By means of an in vitro bioassay technic described at the last meeting of the Society, it has been possible to investigate the effect of various agents on the incorporation of C^{14} from labeled acetate into lipids synthesized by the aorta.

Estrone, testosterone, hydrocortisone, and p-aminobenzoic acid (PABA) have each been studied separately. The male sex hormone increases the incorporation of C^{14} into all the classes; the female sex hormone primarily promotes the incorporation of C^{14} into the classes of which phospholipids form a part. Hydrocortisone increases the incorporation into the classes containing, in part, both cholesterol and cholesterol esters.

In addition to these observations, a study is being made of the capacity of the blood vessels to metabolize the hormones.

PABA affects C^{14} incorporation in the same fashion as estrone. However, perfusate analysis indicates that the vitamin may have the additional capacity to increase movement of phospholipid-containing classes out of the aorta and into the perfusate.

9:30 Discussion

9:45

16. Electron Microscopic Study of Arterial Endothelium

Robert C. Buck. From the Department of Microscopic Anatomy, University of Western Ontario Medical School, London, Canada.

The inner surface of the endothelial cells has been particularly studied. This surface shows multitudes of small vesicles which appear as pockets projecting into the cytoplasm from the plasma membrane. These resemble elements of the endoplasmic reticulum. Larger pockets run for considerable distance into the endothelial cells and, in turn, have the smaller ones projecting from them. It has been possible to show a continuity of the larger pockets with the blood vascular lumen by means of the injection of colloidal thorium dioxide intravenously.

Feeding rabbits with cholesterol results in the production of large cisternas in the endoplasmic reticulum filled with relatively electron-scattering material, possibly lipoprotein. The possibility that the small vesicles or pockets seen in normal endothelium are converted to the endoplasmic cisternas is being studied. If this is so, it suggests a pathway by which the lipoprotein may enter these cells, i.e., through the numerous small vesicles at the surface.

The intercellular cement lines are also being studied. These are relatively simple boundaries in normal arteries consisting of a narrow space between the plasma membranes. They become convoluted and the space between them enlarges irregularly in cholesterol-fed rabbits.

9:55 Discussion

10:00

17. Biological Observations on Denatured Serum Lipoproteins

L. L. Waters. From the Department of Pathology, Yale University School of Medicine, New Haven, Conn.

Clear human serum (cholesterol 250 to 280 mg. per cent) injected intracorneally in anesthetized dogs left a sudanophilic residue in the stroma after the subsidence of edema. Control dog serum (cholesterol 65 to 125 mg. per cent) did not. Clear serum from dogs after cholesterol feeding (cholesterol 250 to 350 mg. per cent) deposited a lipid-staining material in the cornea similar to that following the injection of normal human serum.

Clear human serum dried from the liquid state in vitro and subsequently reconstituted to volume developed turbidity due to insoluble lipoprotein complexes. Clear dog serum (low cholesterol) contained only traces of this material. As the serum cholesterol values in cholesterol-fed dogs increase, the amounts of lipoproteins denatured by the standard drying procedure also increased. At cholesterol levels between 250 to 350 mg. per cent, 10 to 15 per cent of the total serum cholesterol was present in the denatured fraction. When the serum cholesterol level was 400 mg. per cent, up to 30 per cent of the total was found in the insoluble residue.

The denatured lipoprotein complexes derived by drying from normal human serum or from the serum of hypercholesterolemic dogs, when sus-

ended in saline and injected intracorneally, gave ise to lipophage reactions morphologically like hose occurring in arteriosclerosis in man.

When dogs were fed a high-cholesterol, high-fat liet, not only did their serum cholesterols increase, but also their denaturable serum lipoproteins, as indicated. At this time, if injury of their coronary rteries was instituted (allylamine), fatty, foam-cellular intimal granulomas developed at the sites f arterial injury. This transformation occurred regularly at serum cholesterol levels of 250 to 350 ng. per cent. In dogs fed high-fat, low-cholesterol diets, without elevated levels of serum cholesterol or of denaturable lipoproteins, fatty arterial granulomas did not develop, although transient deposition of lipid at the injured sites could be demonstrated.

The present observations emphasize the need for comprehensive studies of the basic physical and chemical factors that affect the solubility of serum lipoproteins in the artery wall.

10:10 Discussion
10:15

18. Sex Differences in the Biochemistry of Rat Biopsy-Connective Tissue

Robert J. Boucek, Nancy L. Noble and Kung-Ying T. Kao. From the Howard Hughes Medical Institute, Miami, Fla.

Aging and atherosclerosis have at least one thing in common; both processes occur in connective tissue. A sex difference in the incidence of atherosclerosis has been demonstrated in humans, but no quantitation of the sex differences in aging of humans has been possible. The purpose of this report is to record sex differences in the biochemistry of rat connective tissue obtained by the sponge-implantation technic. All data are expressed on a content basis, i.e., milligram or gram per gram of implanted sponge, to obviate any variation in water content.

Connective tissue contains large amounts of lipids, including cholesterol. No significant sex difference in lipid content of rat connective tissue was observed. Studies of the in vitro incorporation of C^{14}-acetate into cholesterol indicated a significantly greater incorporation in the tissue obtained from the male rat than in the female tissue (7019 ± 3785 c.p.m./Gm. sponge; 4638 ± 3228 c.p.m./Gm. sponge).

The collagen content of biopsy-connective tissue obtained from the male rat was found to be greater than that of the female. After the initial 21 days of connective tissue growth in the female rat, no further increase in the amount of collagen occurred even after 1 year while the collagen content in the tissue of the male rat continued to increase even after 300 days of tissue age. When the incorporation of C^{14}-lysine and its conversion to hydroxylysine were followed as an index of the metabolic activity of collagen, it was noted that the collagen obtained from the female rat maintained a high specific activity during the period of 21 to 300 days of tissue growth. Collagen of the 300-day-old tissue of the male rat was only 37 per cent as active as that of the 21-day-old tissue and approximately 65 per cent as active as that of the 300-day-old female tissue. This suggests that the degradation of collagen equals the active rate of collagen synthesis in the female. The turnover of collagen in the male appears to be less than in the female, and the rate of degradation is slower than the rate of synthesis.

Castration of the male rat caused a reduction in total collagen content of connective tissue while oophorectomy of the female rat did not affect collagen content.

Approximately 30 per cent of the collagen is solubilized by 0.5 M acetic acid. It was the acid-soluble collagen which varied with sex and gonadectomy in the male rat. The contents of acetic acid-insoluble collagen in the tissues from the male, female and gonadectomized animals were constant.

10:25 Discussion
10:30

19. Hypercholesterolemia of Starvation as Related to Changes in Plasma Volume

H. Yacowitz, S. G. Kahn, S. Wind and B. Amrein. From the Squibb Institute for Medical Research, Division of Olin-Mathieson Chemical Corp., New Brunswick, N. J.

Total cholesterol levels were determined in the blood serum of roosters starved for periods ranging from 5 to 33 days. Water was available ad libitum during starvation. Cholesterol levels increased rapidly and showed no tendency to plateau. In an experiment in which normal birds were starved for 29 days, serum cholesterol levels were elevated to 333 mg. per cent while controls on full feed averaged 176 mg. per cent. The starved birds lost 35 per cent of their body weight. Determinations conducted after 29 days starvation using the Evans blue dye procedure showed that plasma volume was decrease 73 per cent below unstarved controls. When changes in body weight and plasma volume were taken into account, calculations showed that normal birds on full feed and birds starved for 29 days had similar levels of total serum cholesterol per 100 Gm. of body weight. No difference in total liver cholesterol was noted. Roosters fed thiouracil prior to starvation showed serum cholesterol levels of 365 mg. per cent after 33 days. Decreased plasma volume accounted in large part for the apparent increase in cholesterol.

Daily oral dosage of normal birds with 20 or 30 ml. of linseed oil during starvation reduced serum cholesterol levels 13 and 21 per cent respectively. When linseed oil dosage was terminated serum cholesterol promptly increased to levels equal to

those found in starved controls. Coconut oil produced little or no decrease in serum cholesterol.

Protein deficiency and certain vitamin deficiencies have been reported to cause hypercholesterolemia in experimental animals. The increased serum cholesterol levels observed in severely deficient animals may be due, at least in part, to a reduction in plasma volume resulting in increased serum concentration of cholesterol.

10:40 Discussion

10:45

20. Dietary Cholesterol and the Endocrine Regulation of Plasma Lipids

N. R. Di Luzio and B. S. Powers. From the Division of Physiology, University of Tennessee, Memphis, Tenn.

Following bilateral adrenalectomy of dogs and subsequent maintenance on DCA, a progressive and marked decline occurs in plasma phosphatide, cholesterol, and lipoproteins which amounts to a mean 50 to 70 per cent reduction in a 4-week period. In view of studies which implicated altered plasma lipid relationships in atherogenesis and to extend our observations to factors which might modify this hypolipemia, cholesterol, or lard in the amount of 1 Gm./Kg./day was fed for 1 month to 6 of 11 adrenalectomized dogs. Plasma samples obtained prior to, and at weekly intervals, were analyzed for phosphatides, cholesterol, and total lipids. In comparison to unsupplemented adrenalectomized dogs, the cholesterol-fed dogs showed the following mean changes: a 185 per cent increase in cholesterol, a 330 per cent elevation in phosphatides and a 145 per cent increment in neutral fat. Thus, cholesterol feeding to adrenalectomized dogs on DCA prevented the characteristic decline in *all* plasma lipid fractions. The feeding of an identical amount of cholesterol to 4 normal dogs produced no alterations in plasma lipids. Supplementing Purina chow with lard was associated with the characteristic hypolipemic state. The mechanism whereby cholesterol not only prevents the hypolipemia following adrenalectomy, but also produces a significant elevation in plasma phospholipid and cholesterol over the preoperative values has not been clarified. Current evidence suggests that cholesterol may exert a specific steroid response. It has been noted that the removal of the testes of the cholesterol-fed adrenalectomized dogs nullifies the hyperlipemic response of dietary cholesterol. These studies emphasize the significant role of the adrenal and testes in the regulation of plasma lipid levels and also stress the intimate relationship which exists between the various plasma lipid fractions.

10:55 Discussion

11:00

21. Enzymatic and Hormonal Control of Fatty Acids Synthesis

G. Cabrera and Menard M. Gertler. From the New York University-Bellevue Medical Center, Institute of Physical Medicine and Rehabilitation and the Department of Biochemistry, New York University College of Dentistry, New York, N. Y.

It has been demonstrated both in vivo and in vitro that alloxan diabetes in rats results in both reduction of fatty acids synthesis and CO_2 production when glucose is used as the substrate. Other investigators have further demonstrated by using liver slices that this impaired lipogenesis could be restored if diabetic animals were treated with insulin for a variable period of time before death. Results obtained by others studying fatty acids synthesis in particle-free liver extracts provided circumstantial evidence suggesting that the supply of reduced pyridine nucleotides to the system was a limiting factor in the over-all yield of fatty acids. On the other hand, several laboratories have reported changes in the activities of several enzymes both of the glocolytic and of the respiratory pathways occurring in the livers of alloxan-diabetic rats. All the effects attributable to insulin seem to us to have these facts in common: (1) they require intactness of the cellular structure and (2) that insulin be given in vivo for several days before the animal is sacrificed.

To extend these observations several types of experiments were carried out in our laboratory using livers of alloxan-diabetic rats, either as (a) slices, (b) whole homogenates, (c) mitochondrial fractions or (d) particle-free extracts. The results with slices and homogenates confirmed earlier findings by others. Studies designed to detect any differences in energy transfers using mitochondrial fractions did not reveal any changes in P/O rations between normal and diabetic rats, using either pyruvate or α-ketoglutrate as the oxidizable substrate. The studies performed with particle-free systems showed an absolute requirement for the simultaneous presence of DPNH and TPNH and a relative (or partial) dependence on any of them. Because during the catabolism of glucose by the nonparticulate systems of the cell TPNH is generated only in the pentose phosphate pathway, the activity of G6P dehydrogenase in these extracts was studied using the isocitric acid dehydrogenase for comparison. It was found that the ration G6PDH/isoCDH was 1.1 for normal and 0.6 for diabetic animals.

The implications of these findings to the metabolism of fatty acids and to the more general problem of atherosclerosis will be discussed in greater detail along side the tentative hypothesis that in the regulation of the cellular metabolism of fats the immediate factors are the levels of oxidized and

reduced pyridine nucleotides and the activities of the related enzymes as well as the levels of intermediate metabolites, all of these factors being dependent on the rate of utilization of glucose by the cell, a process which according to the present evidence seems to be the main if not the only one affected by insulin.

11:10 Discussion
11:15

22. Serum Proteins and Lipids: Relationship of Cholesterol and Hypoalbuminemia

Harold H. Orvis, Marshall H. Jacobson and John M. Evans. From the Department of Medicine, George Washington University School of Medicine, Washington, D. C.

Recent studies have indicated that hypoalbuminemia may be a factor in the hyperlipidemia of nephrosis. However, the precise role of albumin has not been defined. Nevertheless, it seemed pertinent to inquire if hypoalbuminemia predisposes to increased serum lipids in other diseases.

The following report summarizes observations of the serum proteins in relation to serum lipids in 90 subjects. The data were analyzed by punching on Keysort cards the following information: age, sex, electrocardiographic findings, nutritional status, blood pressure and diagnosis together with serum cholesterol and protein fractions determined by paper electrophoresis. The subjects included 11 normals, 25 patients with chronic renal disease, 27 patients with coronary artery disease and 27 with a variety of systemic illnesses.

In thirty of the patients the serum albumin was less than 53 per cent of the total protein or 3.20 Gm. per cent (2 S.D. below the normal mean). Ten of these had hypercholesterolemia exceeding 250 mg. per cent. Of these 10, 4 had renal disease, 2 had had myocardial infarction, 1 had angina pectoris, 1 was hypothyroid and 2 had obstructive jaundice. None were hypertensive or obese. The other 20 patients with hypoalbuminemia had normal or low serum cholesterol.

On the other hand, 54 of the 90 subjects had normal serum albumin. In this group there were 17 with elevated serum cholesterol, none of whom had renal disease and only 3 with myocardial infarction. Of the remaining 41 patients with normal cholesterol, there were 7 with myocardial infarction. Obesity and hypertension were proportionately divided between the hyper and normocholesterolemic groups.

Of the 90 subjects there were 29 with hypercholesterolemia, most of whom were over 45 years of age. In 10 of these serum albumin was low by 2 S.D. and in 2 by 1 S.D. The other serum protein fractions bore no consistent relationship and in none was the β fraction increased.

There were 27 of the 90 subjects with angina pectoris or myocardial infarction. In 5 serum albumin was depressed 1 S.D., 12 had elevated serum cholesterol and 3 had both abnormalities.

In summary, one third, or 30 of the 90 subjects manifested decreased serum albumin and in only 10 of these was there hypercholesterolemia. However, about one third, or 29 subjects of the group studied had hypercholesterolemia. Since in only 10 subjects was there both hypoalbuminemia and hypercholesterolemia, it is concluded that this relationship is not significant.

11:25 Discussion
11:30

23. Studies on Genetic and Environmental Control of Serum Cholesterol Level

David Adlersberg, Louis E. Schaefer and Arthur G. Steinberg. From the Mount Sinai Hospital and Central Manhattan Medical Group, New York, N. Y.

This study concerns the role of heredity and environment in determining the level of serum cholesterol. It is based upon analyses of 201 families, 402 parents and their 373 children, totalling 775 individuals, who were selected at random from a group of New York City employees of low-middle income. On the basis of previous investigations one would expect an increased frequency of hypercholesteremia (defined as the upper 5 per cent level of this population) among the children of families in which a parent was hypercholesteremic. The frequency of hypercholesteremia was 17 per cent among the 36 children who had a hypercholesteremic parent; it was 2 per cent among the 337 children of normocholesteremic parents. The probability that this difference is due to sampling is less than 0.01. Detailed genetic analysis indicates that the data are compatible with a previously-reported hypothesis that hypercholesteremia is due to a dominant gene with incomplete penetrance, and that penetrance increases with age.

The correlations of serum cholesterol levels were as follows:

Correlation coefficients*

Item	N	r	p
Mother-father	201	.0056	$>.2$
Father-child	373	.2101	$<.001$
Mother-child	373	.3646	$<.001$
Sib-Sib†	123	.3701	$<.001$

*All cholesterol levels were converted to equivalent levels for males aged 20 to eliminate factors of age and sex.

†Intraclass r based on first 2 sibs only.

The data indicate that the serum cholesterol levels of fathers and mothers were unrelated;

whereas the levels of the children were significantly associated with those of the parents, and the levels of the siblings significantly related to each other.

The parent-child and sib-sib correlations, when compared with the lack of mother-father correlation, adds further evidence to the concept that serum cholesterol levels are genetically determined. The independence of the cholesterol levels of the parents indicate that the common environment shared by a family does not lead to common cholesterol levels unless blood relationship exists.

The level of serum cholesterol is distributed throughout this population as a continuous variable. It may be postulated that serum cholesterol concentration at any level is genetically determined. This does not exclude the possibility that environmental factors affect serum cholesterol levels in various population groups. On the other hand, these data are compatible with the concept that genetic factors may represent a predisposition to atherosclerosis.

11:40 Discussion

11:45 Preliminary Report of the Committee on Grading of Atherosclerotic Lesions, R. L. Holman, Chairman

12:00

Luncheon, First George Lyman Duff Memorial Lecture, William Boyd

2:00

Business Session

2:30

Presidential Address, Charles F. Wilkinson, Jr.

Prometheus and Pandora

SUNDAY AFTERNOON

R. Gordon Gould, Presiding

3:00

24. Effects of Ischemia on the Human Renal Glomerulus: Natural History of the Lesion and its Relation to Hypertension

J. F. A. McManus and C. H. Lupton. From the Department of Pathology, University of Alabama Medical Center, Birmingham, Ala.

MacGregor in 1930 described changes in the glomeruli of individuals with hypertension as a wrinkling of basement membrane of the glomerulus leading to simplification. She pointed out that individuals with hypertension had glomerular scars which she called hypertensive contracted glomeruli and that in early cases it is more reasonable to look for hypertensive glomeruli than to look for arteriolar disease. She recalled that Klemperer and Otani had described the same changes in the glomerulus and related them to ischemia rather than to hypertension.

Renal biopsy studies have emphasized the necessity for glomerular changes being recognized rather than the changes in the arterioles. Castleman and Smithwick, for example, in 1943 had found that clinical hypertension preceded vascular disease recognizable in tissue sections. The present report recapitulates our knowledge and studies on the ischemic glomerulus as regards histology and histochemistry. It describes in detail the natural history of the changes in the ischemic glomerulus as seen in histologic and histochemical preparations and relates these changes to the presence or absence of clinical hypertension. Glomerular changes of ischemia, it is emphasized, are present and diagnostic before histologically recognizable vascular changes are produced in the kidney. This is in keeping with the physiologic observation in the changes of renal blood flow in "essential hypertension" and recognizes the fact that the physiological changes in the caliber of the vessels are not readily appreciated in routine histologic preparation.

3:10

25. Experimental Association of Hypertension with Hypertensive Disease

G. M. C. Masson, L. J. McCormack and Harriet P. Dustan. From the Research Division and Department of Pathology, Cleveland Clinic Foundation and Frank E. Bunts Educational Institute, Cleveland, Ohio.

Present widespread use of antihypertensive drugs is predicated on the view that hypertension as such is the major cause of hypertensive vascular disease. This postulate had had some experimental support (Byrom and Wilson). However, Koletsky has recently demonstrated hypertensive vascular disease in rats with renal infarction, although these had been given Dibenamine as an antihypertensive agent. Sequential data on arterial pressure were not made available.

The present re-examination of this problem used Koletsky's technic for induction of acute renal hypertension, but substituted hydralazine (Apresoline), a definitely effective antipressor drug, for Dibenamine.

Among 13 rats with renal infarction, 9 showed arterial necroses at the eighth day; maximum blood pressures in these ranged over 155 mm. Hg and in 4 of them were over 190. Pressures in the 4 rats without lesions ranged from 110 to 180 mm. Hg.

Among 15 rats with renal infarction given hydralazine by lavage only 3 showed lesions. In these there were wide fluctuations of pressure from low levels immediately after treatment, up to 200 mm. Hg on the following day. Six rats similarly prepared, but given hydralazine in drinking water, showed more stable pressures; vascular necroses occurred in 3, in association with pressures up to 175. Seven of 8 rats similarly prepared, but given hydralazine both by gavage and in drinking water, maintained pressures under 150 mm. Hg; 1 reached 175 mm. Hg. One of this group showed a vascular lesion, namely myocardial necrosis. The only vascular lesions seen in sham operated rats (blood pressure 130–150 mm. Hg) were focal areas of vascular cuffing and granulomata around accidentally implanted fur; these might readily be confused with those of hypertensive splanchnic arteritis.

It is concluded that increased arterial pressure as such is an important factor in the genesis of hypertensive vascular disease, the more so since experiments in progress indicate that hydralazine treatment promotes healing of the lesions of hypertensive vascular disease.

3:20 Discussion

3:30

26. The Cholesterol and Phospholipid Relationships in Serum Lipoproteins

Herbert J. Kayden and J. Murray Steele. From the Research Service, Third (New York University) Medical Division, Goldwater Memorial Hospital, New York, N. Y.

We have previously reported that, on the average, sphingomyelin accounted for 10 per cent of the phospholipids in the α fraction and 25 per cent in the β fraction of the lipoproteins of human sera. Further studies have shown a remarkable constancy in the ratio between cholesterol and sphingomyelin in both of these fractions. In the α fraction, each milligram of cholesterol is associated with 0.14 $\pm$ .06 mg. of sphingomyelin; in the β fraction each milligram is associated with 0.16 $\pm$ .04 mg. of sphingomyelin.

The lipoproteins were isolated by zone electrophoresis using starch as a supporting medium. The distribution of total cholesterol between α and β lipoproteins was in accord with the values reported by others using different technics of separation (Cohn fractionation, ultracentrifugation, paper electrophoresis, etc.) for groups of young individuals, older persons and patients with atherosclerosis. The distribution of sphingomyelin between α and β-lipoprotein fractions closely paralleled the partition of cholesterol between these fractions in each individual serum, and over a wide range of serum cholesterol levels and α/β-lipoprotein ratios as determined from the cholesterol content of these fractions.

The effects of synthetic estrogens and androgens upon the serum lipoproteins were studied in a small group of patients. The usual estrogenic effect was an increase of cholesterol in the α lipoprotein fraction with little change or a decrease of cholesterol in the β fraction. The change in distribution of sphingomyelin in α and β fractions followed very closely the change in cholesterol partition.

In a previous report we have observed that sphingomyelin is only a small fraction (<10 per cent) of the total phospholipid in young, normal aortas, but as aging and/or atherosclerosis occur, it becomes the major component of the phospholipids of the arterial walls and plaques. In view of the close relationship between the cholesterol and sphingomyelin content of the 2 fractions of serum, the study of the relationship of these same compounds in the saline-soluble lipoproteins isolated from arterial walls may be of considerable importance.

3:40 Discussion

3:45

27. Serum Lipid and Lipoprotein Response to Therapy of Abnormal Thyroid Function and to Triiodothyroacetic Acid (Triac) Administration in Euthyroid Subjects

Robert H. Furman, R. Palmer Howard and Leonard N. Norcia. From the Cardiovascular Section and the Section on Endocrinology and Metabolism, Oklahoma Medical Research Foundation, and the Departments of Medicine and Biochemistry, University of Oklahoma School of Medicine, Oklahoma City, Okla.

The alterations in serum lipids associated with abnormal thyroid function have long been of interest in relation to atherosclerosis. Serial observations of serum lipids and lipoproteins have been made in 8 (all female) hypothyroid and 11 (9 female) hyperthyroid patients during treatment. Lipoproteins were determined by refractometric analysis during ultracentrifugation, solvent density 1.21 Gm./ml.

The hypothyroid group manifested significantly higher mean values for total and unesterified cholesterol concentrations, C/P ratios, high density, $-S_{1.21}$ 0–20 (α) and lower density $-S_{1.21}$ 25–40 (S_f 12–20 or β) lipoprotein levels. Low density $-S_{1.21}$ 40–70 and >70 (S_f 12–20 and >20) lipoprotein concentrations were greater in the hypothyroid group, but the differences were not significant.

Although the hypothyroid subjects had greater concentrations of both lower density β and high density α-lipoproteins, α/β-lipoprotein ratios were low in this group, indicating that the bulk of the lipid was transported as a lower density lipoprotein.

In this group therapy typically led to reduction in all lipid fractions, most marked with respect to the β-lipoprotein levels, and a return of the α/β-lipoprotein ratio toward unity. Of interest is 1 patient who was noted to have hyperlipemia associated with marked increase in low density $-S_{1.21}$

40 or greater lipoproteins. While triiodothyronine and thyroid extract produced the anticipated reduction in serum cholesterol, phospholipid, $-S_{1.21}$ 0–20 and 25–40 lipoprotein levels, with return of the α/β-lipoprotein ratio toward unity, the concentration of low density $-S_{1.21}$ 40–70 and >70 lipoproteins, although reduced by treatment, nonetheless remained at abnormally high levels.

In the hyperthyroid patients, treatment resulted in an increase in all lipid fractions, with relatively little change in α/β-lipoprotein ratios.

In 3 euthyroid subjects, 1 of whom had mild hypercholesterolemia (300–330 mg. per cent), triiodothyroacetic acid produced marked reduction in cholesterol, attributable mainly to reduction in β-lipoprotein concentrations.

3:55 Discussion

4:00

28. Metabolism of Bile Acids in the Dog

Erwin H. Mosbach and Forrest E. Kendall. From the Columbia University Research Service, Goldwater Memorial Hospital and the Departments of Biochemistry and Medicine, Columbia University, N. Y.

It has previously been reported that euthyroid dogs respond to high cholesterol diets by a 5-fold increase in fecal bile acid excretion, while in thiouracil-treated animals, the administration of excess dietary cholesterol produced only a 2-fold increase of bile acid output. Because of the structural change undergone by the bile acids during passage through the intestinal tract, studies dealing with the fecal bile acids yield little information concerning the effect of cholesterol and thiouracil upon the nature of the bile acids produced. For this reason, studies were carried out on the type and concentration of bile acids in gallbladder bile and fistula bile of dogs maintained on various experimental regimens. It was found that thiouracil-treated dogs receiving high cholesterol diets had the same concentration of cholesterol and of total bile acids in their gallbladder bile as euthyroid dogs receiving a low cholesterol stock diet. However, animals maintained on the cholesterol plus thiouracil regimen had a significantly lower cholic acid/deoxycholic acid ratio in gallbladder bile than dogs fed the stock diet with or without thiouracil. This difference could not be ascribed to a lowered rate of conversion of deoxycholic acid to cholic acid because this study showed that the dog, unlike the rat, does not convert deoxycholic acid to cholic acid. Experiments with cholecystonephrostomized dogs demonstrated that their bile acid excretion (600 mg./day) cannot be increased by the administration of cholesterol (or cholesterol plus cholic acid to facilitate absorption of the sterol). In these animals evidence was obtained that exogenous bile acids can regulate bile acid synthesis by the liver.

4:10

29. Enterohepatic Circulation of Bile as a Factor in the Regulation of Hepatic Cholesterol Synthesis in Dogs

C. Bruce Taylor, Stephen G. Economou, LaVerne Cox, F. B. Kelly, Jr. and G. E. Cox. From the Department of Pathology, Presbyterian-St. Luke's Hospital, Chicago, Ill.

An in vitro incubation technic was used to estimate the rate of cholesterol synthesis, from l-C^{14}-sodium acetate, in viable liver biopsies surgically removed from dogs. The enterohepatic circulation of bile was eliminated through biliary stasis (common duct ligation) and biliary fistulas (cholecystopyrelostomy); the enterohepatic circulation was increased by dietary supplementation with bile and bile acids. Synthesis rates were calculated as milligrams of newly synthesized cholesterol per 100 Gm. of liver per hour. Hepatic cholesterol synthesis rates in 21 control dogs ranged from 0.2 to 1.2 (average: 0.65) mg./100 Gm./hr. In 6 animals with biliary stasis of 2 weeks duration, synthesis rates ranged from 1.1 to 3.3 (average: 2.4); individual animals showed an average elevation of 4 times their respective control rates. In 8 dogs with biliary fistulas of 3 or more weeks duration, synthesis rates ranged from 1.2 to 3.3 (average: 2.1); individual animals showed an average elevation of 3 times their respective control rates. Preliminary studies have shown no significant effect of daily feeding of canine bile or bile acids upon the synthesis rates of intact dogs. Feeding canine bile to biliary fistula dogs sometimes partially suppressed synthesis rates towards normal. Feeding human bile (with a higher cholesterol content than dog's bile) to intact dogs usually produced slight to moderate suppression of synthesis rates. The effect of dietary bile supplements varied with the manner of feeding and the time interval between feeding and synthesis measurements.

4:20

30. Bile Acid Fractions in Human Bile and their Relationship to Cholesterol Excretion

Robert B. Failey, Jr. and Marion E. Hodes. From the Department of Medicine, Indiana University School of Medicine, Indianapolis, Ind.

Bile acid determinations on human bile were made by the method of Mosbach et al., the 2 fractions measured being the trihydroxy (cholic) acid and the dihydroxy (deoxycholic and chenodeoxycholic) acid. Serum and bile cholesterol was concurrently determined by the method of Zak. Specimens were obtained in series at autopsy. Patients of both sexes with an age range from 28 to 83 years had been hospitalized principally because of a variety of chronic diseases.

Preliminary results obtained from 12 individuals have shown the following: Trihydroxy bile acid,

average 9.32 mg. of acid/1000 mg. of bile, range 1.53 to 20.56 mg. Dihydroxy bile acid, average 15.42, range 1.02 to 40.04. Ratio of dihydroxy to trihydroxy acid, average 1.65, range 0.97 to 4.44. Serum and bile cholesterol, average 145.45 and 358.60 mg. per cent, range 100 to 275 and 30 to 1170 mg. per cent, respectively.

Autopsy observations on these individuals have been made with particular reference to the findings in the arteries, liver, gallbladder, and adrenal cortex. Relationships between autopsy and clinical observations and biochemical determinations will be presented and more closely correlated.

4:30 Discussion

4:45

31. Studies on the Physical State of the Serum Lipids under Stress

D. A. Sherber and M. Marcus. From the Metabolic Research Laboratory, Fordham Hospital, Bronx, N. Y.

The authors previously demonstrated that the adrenals play a role in the physical state of the serum lipids. Bilateral adrenalectomy resulted in an increase in serum lipids and the easily extractable fraction of these substances. Studies done on acutely ill patients immediately after admission to Fordham Hospital demonstrated definite changes in the serum lipid fraction as manifested by an increase in the free unesterified fatty acids of the serum and in the fraction of easily extractable cholesterol. Total serum cholesterol remained relatively unchanged. The fatty acid fraction was in all instances increased 100 per cent of normal, during stress. The easily extractable cholesterol rose to three to four times normal values during stress. Upon recovery, the easily extractable cholesterol fraction returned to normal and there was a definite fall in the free unesterified fatty acid fraction. Studies of 17 ketosteroid and 17, 21 dehydroxysteroid excretion parallel the lipid findings.

Since stress and the recovery from stress are in a large measure dependent upon the homeostatic mechanism of the adrenals, it would appear that the changes noted in the lipids are dependent on adrenal function.

4:55 Discussion

SUNDAY NIGHT

Joseph H. Bragdon, Presiding

7:30 Registration

8:00

32. Further Assessment of the Role of Sitosterol in Accounting for the Plasma Cholesterol Depressant Action of Corn Oil

J. M. R. Beveridge, W. F. Connell, G. A. Mayer and H. Haust. From the Departments of Biochemistry and Medicine, Queen's University, Kingston, Ontario, Canada.

Previous work has demonstrated the presence of a factor in corn oil that actively lowers plasma cholesterol levels (Circulation **12:** 499, 1955). Some workers (Kinsell et al.: Am. J. Clin. Nut. **4:** 285, 1956; Bronte-Stewart et al.: Lancet **1:** 521, 1956) have concluded that the plasma cholesterol depressant effect of such oils may be explained on the basis of degree of unsaturation. We have presented evidence (Fed. Proc. **16:** 11, 1957) that sitosterol accounts for a large part of the activity of corn oil and the present report concerns further work on this problem. Fifty-three normal subjects (46 males and 7 females—university students and faculty members) consumed for 8 days a homogenized ration (no. 1) providing 35 per cent of calories from butter fat and 25 per cent of calories from corn oil. They were then divided into 4 groups. One was continued for a further 8 days on the diet described above. The other 3 groups ate the following modified diets: no. 2, 35 per cent of calories from butter fat plus an amount of sitosterol (dissolved in corn oil) equal to that provided by the corn oil in ration no. 1; no. 3, 35 per cent of calories from butter fat, plus 25 per cent of calories from the least volatile fraction of corn oil; no. 4 as for no. 3 except the sufficient sitosterol was added to bring the level up to the same concentration present in no. 1. The only other items permitted were water, clear tea and clear coffee.

There was no detectable difference in the plasma cholesterol depressant effect of the four rations. These results demonstrate conclusively that the plasma cholesterol depressant effect of corn oil is accounted for in large part by its sitosterol content. The possibility of a synergistic effect between sitosterol and some substance in the corn oil, possibly unsaturated fatty acids, is a possibility that must be entertained.

8:10

33. Effect of Long Chain Polyunsaturated and Saturated Fatty Acids on the Blood Lipids in Man

Louis Horlick. From the Department of Medicine, University of Saskatchewan, Saskatoon, Canada.

Corn oil, ethyl linoleate concentrate and ethyl stearate were added to a basal diet consisting of natural foodstuffs selected for their low fat content. The fat content of the basal diet was 4 per cent of total calories (approximately 10 Gm./day). When the test fats were given to the extent of 40 per cent of total calories, a fall of 25 to 35 per cent in serum cholesterol in 7 to 10 days was noted. A similar drop in cholesterol was observed when the basal diet alone was fed for the same period of time.

In a second study, the test fats were added after a preliminary 2-week period on the low fat basal diet. Neither corn oil nor ethyl linoleate concentrate produced any further fall in serum cholesterol levels when added in increasing amounts up to a total of 80 Gm./day or approximately 25 per cent of total calories. Fecal fat studies showed good absorption of these substances. Ethyl stearate was only absorbed to the extent of 65 to 70 per cent of the dose given (up to 80 Gm./day) and caused a further slight decline in the serum cholesterol levels. Butter fat resulted in a rise in the serum cholesterol level.

Our data indicated that a low fat diet, corn oil or ethyl linoleate, all had a similar quantitative effect in lowering serum cholesterol levels, and that the polyunsaturated fatty acid ester (ethyl linoleate) possessed no special ability in this respect. Neither did ethyl stearate, a fully saturated fatty acid ester, possess any cholesterol-elevating property.

The relatively high levels of serum cholesterol seen with natural diets containing mixed fats may be related to some factor in butter fat, as yet unidentified.

8:20

34. Effect of Corn Oil Feeding on Cholesterol Metabolism in the Rat

Joel Avigan and Daniel Steinberg. From the Section on Metabolism, Laboratory of Cellular Physiology and Metabolism, National Heart Institute, Bethesda, Md.

Studies from a number of laboratories have shown that diets high in corn oil will lower serum cholesterol levels in man and diets high in coconut oil will raise them. The mechanism of this effect has not been determined. The present studies were undertaken to explore the possibility that the effect might be mediated through control of the rate of cholesterol biosynthesis.

Rats kept 17 to 32 days on a diet containing 20 per cent corn oil by weight had significantly lower serum cholesterol levels (74.1 mg./100 ml.) than those receiving 20 per cent coconut oil (81.5 mg./100 ml.) but not lower than the levels in rats on a control diet (70.8 mg./100 ml.). (Each number represents an average of 15 animals.) There was a large and highly significant increase in the concentration of cholesterol esters in the livers of the corn oil fed animals (average 1.66 mg./Gm.) over that in the coconut oil fed group (0.60 mg./Gm.) and in the control animals (0.18 mg./Gm.). There were no significant differences in the concentrations of free cholesterol in the livers.

The rate of cholesterol synthesis in vivo was measured in terms of the uptake of 1-C^{14} acetate injected intraperitoneally 1 hour prior to sacrifice. The total count incorporation into nonsaponifiable lipids in liver and adrenals was increased by more than 100 per cent in the corn oil fed animals as compared with controls or those receiving coconut oil. A large increase in incorporation into serum cholesterol was also observed. These experiments were repeated using the uptake of tritiated water into nonsaponifiable lipids as a measure of the rate of biosynthesis. Essentially similar results were obtained. Because of the increased total amount of cholesterol in the livers of the fat fed animals there are no significant differences when the results are expressed in terms of specific radioactivity, that is, the rate constant for turnover was apparently not affected by the fat feeding.

Corn oil feeding does not decrease but actually increases the rate of cholesterol synthesis and under these conditions the cholesterol lowering effects cannot be due to alterations in rate of synthesis. Studies on the possible effects of corn oil feeding on cholesterol degradation are in progress. The elevation of liver cholesterol in these animals without corresponding elevation, and in some cases with actual depression, of the serum cholesterol suggests an effect of the diet on the partition between the 2 pools.

8:30 Discussion

8:45

35. Pathogenesis of Atherosclerosis in Youth

James A. Maher and Leonard Schreier. From the Department of Pathology, University of Michigan, Ann Arbor, Mich.

The necropsy material at the University of Michigan Hospital for a 10-year-period was reviewed and 65 cases of atherosclerosis in patients under 22 years of age were selected for study. The criteria for atherosclerosis were a significant focal collection of lipid-laden histiocytes and/or cholesterol crystals in the subintimal tissue.

In 22 cases the atherosclerosis was unrelated to any other known disease process and therefore was considered to be idiopathic. In 43 cases it occurred in patients in which an etiologic relationship was suspected; 30 had renal disease, 10 had cardiac disease, 2 had hypertension, and 1 diabetes mellitus.

The gross distribution and histologic appearance of the lesions were noted. The aorta was the most frequent site of involvement regardless of the etiology. Coronary arteries were involved in 50 per cent of the cases of renal and cardiac disease, but showed involvement in less than 10 per cent of the idiopathic cases. Cerebral arteries were frequently involved in patients with renal disease, only occasionally in idiopathic atherosclerosis and were not involved when cardiac disease had been present.

In most cases the plaques were composed chiefly of lipid-containing histiocytes; however, in 4 examples of idiopathic atherosclerosis and 2 of renal disease the plaques showed cholesterol clefts and the intracellular lipid was sparse. In 3 cases of

diopathic atherosclerosis the 2 types of lesions coexisted. The plaques containing the lipid within histiocytes were interpreted as early lesions and therefore probably indicated active atherogenesis. The older lesions showed cholesterol clefts. Where the lesions coexisted it was thought to be an indication that the patient was having a second episode of atherogenesis.

In selected cases histochemical procedures were carried out. Regardless of the etiology of the atherosclerosis, alterations in the acid mucopolysaccharide ground substance occurred adjacent to the lesions and in segments of the vessels distant from the site of atherosclerosis.

8:55 Discussion
9:00

36. Extrathyroidal Effects of Thiouracil on Cholesterol Metabolism of the Rat

Charles H. Duncan and Maurice M. Best. From the University of Louisville School of Medicine, Louisville, Ky.

Induction of hypothyroidism by I^{131} or by thiouracil is a commonly employed adjunct to cholesterol feeding in the production of hypercholesterolemia and experimental atherosclerosis. The method of induction has been found to influence significantly the level of cholesterol in serum and liver produced by cholesterol feeding.

In rats rendered hypothyroid by the prior administration of I^{131} the addition of 1 per cent cholesterol to the diet for a 2 week period resulted in elevation of the mean serum cholesterol to 119 ± 24 mg./100 ml. (normal 72 ± 6). When the hypothyroidism was induced by the addition to the diet of 0.5 per cent thiouracil during the 2 week period of cholesterol feeding the resulting mean serum cholesterol value was 155 ± 38 mg./100 ml. Liver cholesterol differed in the opposite direction, being lower in the thiouracil fed group, 1102 ± 331 as compared to 1625 ± 296 mg./100 Gm. (normal 303 ± 6).

Cholesterol feeding of a group of rats receiving thiouracil plus sufficient l-thyroxine to prevent thiouracil goitre (3 μg./100 Gm./day) resulted in serum cholesterol of 132 ± 23 and liver cholesterol of 705 ± 235 as compared to a group fed cholesterol alone with serum cholesterol of 82 ± 12 mg./100 ml. and liver cholesterol of 1224 ± 388 mg./100 Gm.

To further explore these differences 10 rats were subjected to radiation destruction of the thyroid by I^{131}. Fifteen weeks later 1 per cent cholesterol was added to the diet for a 2 week period. Five animals received, in addition to the cholesterol, 0.5 per cent thiouracil in their feed. At the end of the 2 weeks the mean serum cholesterol of the group receiving thiouracil was 133 ± 24 mg./100 ml. and that of the nonthiouracil-fed group 109 ± 8. The liver cholesterol levels again differed in the opposite direction being 1151 ± 351 in the thiouracil fed group and 1502 ± 297 mg./100 Gm. in the control group.

It is concluded that thiouracil exerts an effect on cholesterol metabolism which is independent of its suppression of thyroid function.

9:10 Discussion
9:15

37. Lipemia as a Cause of Arterial Oxygen Unsaturation, and the Effect of its Control in Patients with Atherosclerosis

Peter T. Kuo and Arthur F. Whereat. From the University of Pennsylvania, Philadelphia, Pa.

We previously observed that fat infusion lowered the oxygen and carbon dioxide content of arterial blood in dogs through its effect on pulmonary gas exchange. This study concerns the effect of fat on arterial blood oxygenation in humans.

Intravenous infusion of 100 to 130 ml. of a 15 per cent commercial fat emulsion in 5 patients with arteriosclerotic heart disease caused a 3.9 per cent to 5.9 per cent decrease in their arterial oxygen saturation. Reflex hyperventilation probably accounted for the concomitant 1.9 to 3.9 volume per cent drop of their arterial carbon dioxide content. Four hyperlipemic patients were studied 5 to 5½ hours following fat ingestion and it was observed that their arterial oxygen saturation decreased from 2.1 per cent to 5.3 per cent without a significant change in their carbon dioxide content.

Control of lipemia in 13 patients with clinical atherosclerosis resulted in improvement in the signs and symptoms of arterial insufficiency (either angina or intermittent claudication or both) in 2 to 8 weeks, depending upon the effectiveness of the method used in lowering their plasma triglyceride levels. Objective evidences of clinical improvement were: a rise in the arterial oxygen saturation, an increase in exercise tolerance, and improvement in the standardized claudication time. Following the control of lipemia for more prolonged periods of time, the following effects were noted in these patients: significant improvement of skin temperature readings with the vasodilatation test, a change from a previously positive to a negative Master's test, and an increase in the amplitude of ballistocardiographic complexes.

These observations support the contention that high concentrations of plasma triglycerides may aggravate or induce arterial insufficiency in patients with clinical atherosclerosis.

9:25 Discussion
9:30

38. Hourly Variations in Serum Total Cholesterol in Normal Males

William Shapiro, E. Harvey Estes, Jr. and Helen L. Hilderman. From the Department of Medicine, Veterans Administration Hospital, and the Department of Medicine, Duke University School of Medicine, Durham, N. C.

The range of the hour-to-hour values for total serum cholesterol has not been established in normal individuals on normal diets. No information is available on the hourly variation in persons whose cholesterol levels have been significantly depressed by dietary means.

Hourly cholesterol values were determined over a 14 to 18 hour period in 10 active healthy young males, 6 on a "normal American" diet and 4 on a rice-fruit diet supplemented with salt and not more than 15 Gm. of butter per day. Total cholesterols were determined by the direct method of Pearson, Stern and McGavack. The standard deviation of a single determination was 3.48 mg. per cent as computed from duplicate determinations on the 151 hourly samples collected during this study.

The mean total serum cholesterol for the 6 subjects on normal diets was 219 mg. per cent. The range of hourly values was relatively narrow, the average standard deviation from the individual's mean being 7.7 mg. per cent. The 4 subjects on the rice-fruit diet were studied after 3 to 5 weeks on the diet, at which point they had experienced and maintained significant falls in serum total cholesterol. The mean value for the group was 142 mg. per cent. The range of hourly values for this group was similarly narrow, the average standard deviation from the individual's mean being 6.7 mg. per cent. The degree of variability was approximately the same in the 2 groups despite the considerable differences in mean cholesterol values.

Activity, rest and meals produced no significant acute effects on the total serum cholesterol. It is concluded from the above data that a random sample of serum total cholesterol will provide a close approximation of the individual's mean value for that day.

9:40 Discussion

9:45

39. Rabbits on Egg Diets

O. J. Pollak. Dover, Del.

Series of rabbits were kept on regular chow and fed 1 egg daily for 21 days. A diet of whole egg or egg yolk (raw) resulted in a threefold increase of blood cholesterol. Feeding of soft boiled egg (2 min./100 C.) or of poached egg (2 min./100 C.) induced a fivefold increase. On a diet of scrambled eggs (1½ min./350 C./1 Gm. butter per egg) blood cholesterol increased 6 times. Feeding of hard boiled eggs (8 min./100 C.), of eggs baked in the shell (30 min./450 C.), or of eggs baked into cakes with chow (30 min./450 C.) resulted in a tenfold rise of blood cholesterol. A diet of fried eggs (1½ min./350 C./1 Gm. butter per egg) caused fourteenfold elevation of hemocholesterol.

Should human beings respond to various egg dishes in similar fashion as the rabbit a revision of many of our ideas about diets would be warranted.

9:55 Discussion

MONDAY MORNING

L. L. Waters, Presiding

8:30 Registration

9:00

40. Clinical Studies with Unsaturated Fats in Patients with Hypercholesterolemia and Hyperlipemia

Richard C. Bozian, Ira J. Laufer, Leonard J. Stutman, Kurt Hirschhorn and Charles F. Wilkinson, Jr. From the Department of Medicine, New York University Post-Graduate Medical School and the Fourth Medical (N.Y.U.) Division, Bellevue Hospital, New York, N. Y.

It has been reported by several investigators that fats rich in unsaturated (essential) fatty acids have lowered serum cholesterol. Most studies have been performed with the use of isocaloric diets and the substitution of the unsaturated fat for the usual fat in the diet.

We have studied the clinical and laboratory effect of a 65 per cent emulsion of safflower oil on patients with several varieties of hypercholesterolemia, with and without hyperlipemia and xanthomatosis. These subjects were ambulatory and no alteration of their diet was attempted, other than the addition of the safflower oil.

Hypocholesterolemia effects were obtained but were not always sustained in spite of continued administration. However, there were instances of decrease in the size of xanthomata even in the face of continued hypercholesterolemia. This raises the consideration that the serum cholesterol level may not necessarily reflect the total body dynamics at any given time with respect to lipid metabolism.

9:10

41. A Comparison of the Effects of β-Sitosterol and Safflower Oil, Alone and in Combination, on Serum Lipids of Humans: A Long-Term Study

John W. Farquhar and Maurice Sokolow. From the Department of Medicine, University of California School of Medicine, San Francisco, Calif.

The present study was designed to compare the action of β-sitosterol and safflower oil, alone and in combination, on serum lipids of humans. Safflower

oil is a highly unsaturated vegetable oil containing 70 per cent linoleic acid and virtually no linolenic acid, tocopherol, or phytosterol.

Fifteen outpatients, average age 48, were maintained on a constant intake of total calories (average 2,340) and fat (average 103 Gm.) for 38 to 52 weeks.

Phases I, III, V, and VII were control periods, with an average intake of 92 Gm. of animal and hydrogenated fat and 11 Gm. of vegetable oil. Safflower oil 81 Gm./day in substitution for animal fat, or β-sitosterol (Cytellin, Lilly) 18 Gm./day were given in random during phases II and IV. In phase VI a combination of β-sitosterol and safflower oil were given. Each experimental phase lasted approximately 7 weeks.

Weekly serum samples were analyzed for total cholesterol, α-lipoprotein cholesterol (ALPC) and β-lipoprotein cholesterol (BLPC) (method of Anderson and Keys). Representative samples were analyzed for total lipids (method of Bragdon), and for phospholipids. Triglycerides were calculated by difference.

The results revealed a rapid and sustained decrease in serum total lipids, phospholipids, cholesterol, and BLPC. Changes in ALPC and serum triglycerides were not significant. The average fall in BLPC was 46 mg./100 ml. (20 per cent) following β-sitosterol, 47 mg./100 ml. (20 per cent) following safflower oil, and 72 mg./100 ml. (32 per cent) after the combination of the two. Inter and intraindividual response was most variable during the safflower phase and least variable during the combination phase. Average body weight varied by less than 1 Kg. throughout all periods. ALPC and BLPC values varied by less than 3 per cent during the 4 control periods.

The results confirm previous findings on the action of β-sitosterol in humans and reveal that changes of a similar magnitude occur when safflower oil is given in substitution for animal fat. The magnitude of the decrease with the combination, although not additive, was 60 per cent greater than that observed with either agent alone. It is concluded that the effect of safflower oil upon serum lipid concentration depends largely on factors other than its content of sitosterol.

9:20

42. Effect of a Formula Diet Containing Various Vegetable Oils upon the Serum Lipids of Human Subjects

Alfred Steiner, Aristides Varson and Daniel Rudman. From the Research Service, First (Columbia University) Division, Goldwater Memorial Hospital, Department of Hospitals and the Departments of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.

Groups of normal, atherosclerotic, and hyperlipemic patients were studied during (1) an initial 2 month period of regular hospital diet, (2) a 2 month period of a safflower seed oil formula diet, (3) a 3 to 5 month period of the regular hospital diet and (4) a final 2 month period of a coconut oil formula diet. The 2 different formula diets contained from 65 to 120 Gm. of 1 of the 2 vegetable oils tested in addition to protein and carbohydrate which were adjusted to meet caloric requirements. The safflower seed oil is a highly unsaturated oil, while cocoanut oil is largely saturated.

In all except 1 of the patients who were placed on the safflower seed oil formula diet, the following changes in the serum lipids were observed. The level of serum cholesterol and phospholipids showed a mean decrease of 21 per cent and reached a base line in 10 to 15 days which was maintained as long as the diet was given. Simultaneously, a 5 to 7 per cent decrease in β-lipoproteins occurred as determined by paper electrophoresis. Chemical analysis showed that the decrease in cholesterol content of the β-lipoproteins equaled or exceeded the fall in total serum cholesterol. During the administration of the safflower oil formula diet, the concentration of linoleic acid in the serum increased by as much as 100 per cent.

When the patients were returned to the regular hospital diet, the serum cholesterol, serum phospholipids, and cholesterol content of the β-lipoproteins increased slowly over a 3 to 5 month period but did not reach the control levels. The β-lipoprotein concentration returned to the control level in a few days. The serum linoleic acid gradually decreased over the same period while an increase occurred in the serum concentration of arachidonic acid.

When the patients were placed on a cocoanut oil formula diet, the serum lipids increased rapidly to control levels.

9:30 Discussion

9:45

43. Hexosamine and Cholesterol Content of the Rabbit's Aorta in Experimental Cholesterol Atherosclerosis

Gardner C. McMillan and Bernard I. Weigensberg. From the Department of Pathology, Pathological Institute, McGill University, Montreal, Canada.

There is a considerable body of evidence relating to changes in the ground substance of the intima of the aorta in atherosclerosis. These changes have largely been studied histochemically. Their interpretation is not agreed upon.

The following experiment reports on the hexosamine and cholesterol content of the aorta in normal and cholesterol-fed rabbits. At the time of writing, 22 normal and 59 cholesterol-fed animals have been studied. The latter rabbits were fed for periods of from 1 to 14 days or for 84 days. After suitable preparation 2 samples of aorta were removed, 1 from the arch and 1 from the bifurcation. Together they constituted about 15 per cent of the weight of

the aorta. They were analyzed for hexosamine by the method of Boas (J. Biol. Chem. **204:** 553, 1953). The remainder of the aorta was analyzed for cholesterol. It is hoped to report on an additional 12 control and 70 experimental animals.

The results indicate no change in the hexosamine content of the aorta, either at the arch or bifurcation, during the experiment. On the other hand, the content of cholesterol in the aorta had doubled after 14 days of cholesterol feeding and was increased 9 times after 84 days of feeding.

The results, like those in man (Kirk, J. E., and Dyrbye, M., J. Gerontology **11:** 273, 1956), fail to establish the role of hexosamine in relation to atherogenesis. The results do not permit comment on the possible occurrence of changes in the mucopolysaccharide ground substances that may not be reflected by hexosamine analysis, on polymerization effects, or on the possible occurrence of localized changes of microscopic dimensions, nor do the results permit comment on hexosamine in relation to fibrotic lesions.

9:55 Discussion

10:00

44. New Method for Estimation of Serum β-Lipoproteins

Edwin Boyle, Jr. From the Department of Medicine, Medical College of South Carolina, Charleston, S. C.

A new chemical method of selective precipitation of β-lipoproteins with subsequent quantitative estimation by simple turbidometric measurements has been developed.

This new method entails the addition of 0.2 ml. serum to a phosphate buffered dilute solution of potassium agar and measuring the optical density of the resulting precipitate. This precipitation is reversible by pH alteration and apparently does not denature or alter these lipoproteins. This method may also be used to obtain quantities of β-lipoprotein for experimental studies.

The values in various animal species and normal humans, grouped according to age and sex, have been determined. Various lipid metabolic errors such as hyperlipemia, hypercholesterolemia and xanthomatosis can be characterized utilizing this new method. These data are comparable to values obtained for β-lipoprotein levels utilizing differential preparative ultracentrifugation and chemical analysis of such fractions, and with separation of serum lipoproteins by paper electrophoresis.

10:10 Discussion

10:15

45. Morphologic Evidence and Significance of Permeation in the Genesis of Arteriosclerosis

M. Daria Haust and Robert H. More. From the Department of Pathology, Queen's University, Kingston, Ontario, Canada.

A year ago we discussed the role of fibrin thrombi in the genesis of the common white plaque in arteriosclerosis. It was shown that one way by which plasma proteins (mainly fibrin) participate in building up arteriosclerotic lesions is by means of superficial encrustation with subsequent organization.

Our further studies provide evidence for the frequent role of permeation of the intima by serum proteins in the development of many phases and types of arteriosclerotic thickenings. In addition to aortic lesions we have studied sections from coronary arteries of 90 hearts, taken at 6 standard sites.

Besides the usual white or yellow arteriosclerotic plaques, glassy, gelatinous circumscribed or diffused thickenings were frequently found. Microscopically they consisted of a purely serous or sero-fibrinous insudate. Sometimes, particularly in the coronary vessels, these changes were not visible grossly but were found only on microscopic examination. Further changes result secondary to the permeation: small insudates separate widely the connective tissue fibers, whereas a larger one causes in addition, fragmentation and distortion of collagen fibers and complete lysis of elastic and reticular fibers. The swelling of ground substance results in a relative diminution in the intensity of metachromasia. Early repair is indicated by an intense increase of metachromasia followed later by formation of reticular and elastic fibers. The last to be formed are the collagen fibers. With the "collagenization" of the area the amount of reticular fibers decrease followed by a second (absolute and final) disappearance of metachromatic ground substance. The outcome of this process is a white, sclerotic, either localized or diffuse plaque, resembling in quality the white plaque of thrombotic origin. Similar changes of permeation with subsequent "conversion" were an almost invariable accompaniment of the tissue overlying well developed atheroma.

Whatever be the role of lipid in the intima these observations emphasize the role of permeated protein in forming a matrix which contributes a large part of the substance out of which many of the arteriosclerotic thickenings result.

10:25 Discussion

10:30

46. Intramural Hemorrhage in Coronary Arteries

Thomas M. Blake. From the Department of Medicine, University of Mississippi School of Medicine, Jackson, Miss.

The forces responsible for converting a hitherto asymptomatic arterial atheroma into the site of a potentially catastrophic acute occlusive lesion are not known, but there is much evidence to indicate

that hemorrhage, either active or passive, in the depths of the lesion may be an important factor. The present study was undertaken to determine the incidence of such hemorrhages in human coronary arteries in a random sample of the autopsy series in a general hospital.

A technic modified from that of Winternitz has been used. The vessels and their vasa vasorum have been injected with india ink, the adventitia removed, and the whole specimens mounted segmentally in clear plastic blocks to permit their examination stereomicroscopically. The first 42 patients so studied have included 22 men and 11 women 45 years of age or older, and 4 men and 5 women younger than 45. The youngest patient was 12 years old and the oldest 87. In the series as a whole the incidence of intramural hemorrhage in the coronary arteries has been 36 per cent; in men 45 years of age or older, 59 per cent; and in women 45 or older, 18 per cent. In no case has such hemorrhage been found in patients less than 45 years old. Intimal vasa vasorum have been demonstrated in the hemorrhagic areas in some instances and not in others.

Findings will be correlated with clinical and autopsy diagnoses. The desirability of study of the coronary arteries as complicated organs, dependent on their blood supply like all organs, will be emphasized.

10:40
10:45

47. Effect of Cerebroside Preparations on Excretion of Fecal Cholesterol

K. K. Carroll. From the Collip Medical Research Laboratory, University of Western Ontario, London, Canada.

Crude preparations of cerebrosides from either beef brain or spinal cord promote the excretion of cholesterol in the feces when fed to rats in sterol-free synthetic diets (Jones, R. J. and Reiss, O. K.: Circulation **12:** 496, 1955. Carroll, K. K. and Noble, R. L.: Canadian J. Biochem. & Physiol.: **34:** 981, 1956). Appreciable effects may be obtained by incorporation of as little as 2 per cent by weight of the cerebroside preparations into the diets. The increased sterol excretion may be partly due to the increased bulk of feces resulting from poor absorption of the cerebrosides, but the concentration of sterol in the feces is also raised. The fatty acid fraction obtained by hydrolysis of the crude cerebrosides also increased fecal cholesterol excretion, but seemed to be less active than the unhydrolysed preparations. The lipid-soluble bases obtained on hydrolysis appeared to be toxic and were poorly accepted in diets even at the 1 per cent level. Experiments are in progress with preparations of ceramide and psychosine. Solvent fractionation of the crude cerebroside preparations and of the fatty acids derived from them did not appear to localize the effect on sterol excretion to particular fractions.

10:55

48. Regulation of Plasma Cholesterol Levels by Fecal Sterol Excretion

Leon Hellman, Robert S. Rosenfeld, William Insull, Jr. and Edward H. Ahrens, Jr. From the Sloan-Kettering Institute for Cancer Research and Rockefeller Institute for Medical Research, New York, N. Y.

The intestinal excretion of cholesterol has been found to function as a physiologic mechanism by which the plasma cholesterol level can be elevated or reduced. This was demonstrated following the intravenous administration of a tracer dose of cholesterol-4-C^{14} to a patient with hyperlipemia and xanthoma tuberosum. Measurements were then made of excreted radioactivity which reflected net changes in the excretion of cholesterol and its transformation products since the radioactive carbon atom remains permanently fixed in the steroid molecule. By this procedure, a "labeled sterol balance study" was performed and the total excretion of cholesterol could be determined when changes in plasma sterol levels were produced by varying the type of dietary fat.

In response to changing the patient's diet from *ad lib.* feedings to a 40 per cent butter oil formula, plasma cholesterol increased from 478 to 720 mg. (net gain 7.2 Gm.). This was accompanied by a decrease in fecal excretion of sterols of at least 5.4 Gm. When the butter diet was replaced by an isocaloric 40 per cent corn oil formula, plasma cholesterol decreased from 720 to 340 mg. (net loss 11.4 Gm.) and the fecal excretion of cholesterol and its end-products increased by a minimum of 9.6 Gm. Throughout, the plasma and fecal cholesterol specific activities approximated each other, indicating that fecal cholesterol was largely derived from a pool in isotopic equilibrium with plasma sterol.

These data show that the character of the dietary lipids affects the quantity of plasma cholesterol by diminishing or increasing the fecal excretion of cholesterol and its transformation products.

11:05 Discussion
11:15

49. Factors Determining the Hypercholesteremic Response in Patients Fed a Brain Extract

R. J. Jones, Thomas F. Keough, David Cummings and Somner Kraft. From the Department of Medicine, University of Chicago, Chicago, Ill.

Over 50 outpatients with coronary artery disease and varying degrees of hypercholesteremia have been treated for periods of 3 months or longer with an oral emulsion of a previously described alcoholic extract of brain. Clinical observations were made

as well as serial serum cholesterol determinations over a 6 month control period and biweekly during the treatment period. The effect of this material upon the mean serum cholesterol level was significant in two thirds of the cases and occasionally induced a fall of 60 to 100 mg. per cent. In general, the results closely paralleled those reported for β-sitosterol.

Analysis of the results indicated that patients with control levels of serum cholesterol above 300 mg. per cent had a mean fall of 20 per cent in that level; from 250 to 300 mg. per cent, a mean fall of 15 per cent; below 250 mg. per cent, a mean fall of 10 per cent. Thus the greater response is found with higher levels of serum cholesterol, and it was in the last group that most of the failures to respond were seen. The only patient with a high serum cholesterol who failed to respond had gained 4 Kg. of body weight during the treatment period. Of the other patients who failed to respond, a dose of less than 20 Gm./day of the extract was taken, a weight gain of more than 4 lb. occurred, or the original level of serum cholesterol was below 250 mg. per cent. In patients who had been on a prescribed low fat diet, a less dramatic response was usually seen, though in some it was still greater than 25 mg. per cent. Thus the control level of serum cholesterol, the effect of a low fat diet, and the caloric balance are important in predicting the response to this material.

11:25 Discussion

11:30

50. Effects of Soybean Lipositol on Serum Lipids and Lipoproteins

Bernard A. Sachs and Ethel Danielson. From the Medical Division, Montefiore Hospital, New York, N. Y.

We have previously demonstrated that incubation of the alcohol insoluble fraction of whole soybean phosphatide complex (containing ⅔ lipositol and ⅓ cephalin) produces an increase in the migration velocity of β-lipoprotein as demonstrated by paper electrophoresis. This effect is similar to that produced by heparin in vivo or clearing factor in vitro. Extension of these studies after further fractionation of this phosphatide fraction by the methods of Folch, and of Woolley, revealed that lipositol, rather than the cephalin moiety, is the compound responsible for the lipoprotein changes observed.

The in vitro effect on serum lipoproteins was reproduced in vivo in the rabbit after the intravenous administration of an emulsion of the alcohol insoluble lipositol phosphatide. In addition, the intravenous administration of this fraction to the rabbit resulted in a prompt rise (within 30 minutes) in serum total lipid, total cholesterol and lipid phosphorus which decreased by 4 hours and was followed by a secondary rise in the serum lipid partition in 24 hours. The elevation in serum lipids after 1 infusion persisted for 6 days. The prompt elevation in serum cholesterol levels is believed to be due to mobilization of lipid from depots rather than an alteration in synthesis, excretion or interference with the reticuloendothelial system. Studies which will evaluate this lipid mobilization effect on the experimental atherosclerotic lesion are in progress. In man, preliminary experiments with the oral administration of this same fraction failed to result in an increase in the migration velocity of β-lipoprotein but did result in a depression of serum cholesterol levels.

11:40 Discussion

11:45

51. Production of Arteriosclerosis in the Rat by ACTH

Bernard C. Wexler and Benjamin F. Miller. From the May Institute for Medical Research of the Jewish Hospital Association of Cincinnati; and the Department of Pathology, University of Cincinnati School of Medicine, Cincinnati, Ohio.

Excesses of adrenal steroids, either because of the inordinate demands made by stressful circumstances or because of functional derangement, e.g., Cushing's disease, is associated with vascular degeneration. Increasing emphasis is being placed on the role of the adrenal glands in hypertension and related cardiovascular-renal degenerative diseases. Although it is reasonable to accept the concept that stress (and adrenal hyperactivity) play a part in the pathogenesis of vascular disease, experimental verification has been incomplete.

The rat, an ideal subject for the study of arteriosclerosis, has been exceptionally resistant to the experimental induction of arteriosclerosis. A few investigators have succeeded in producing arteriosclerotic lesions by employing drastic measures in varying combinations. In addition, the regimen usually must be carried out for an extended period of time before significant vascular degenerative "break through" will take place.

In our experiments, rats fed a regular diet and treated with ACTH developed an explosive type of arteriosclerotic degeneration. This intense vascular degeneration takes place in a matter of weeks. The earliest lesions appear within a week's time of onset of treatment. The distribution of the sclerotic plaques in the rat aorta resembles that seen in the human. In the more severe cases there was extension into the carotids, femoral, and even smaller vessels. A striking sex dichotomy seems to be operative as only females develop these lesions. The male develops other degenerative changes. Gross and histologic specimens will be shown.

11:55 Discussion

MONDAY AFTERNOON

George E. Wakerlin, Presiding

2:00

52. Effect of Large Doses of Nicotinic Acid on Serum Cholesterol and on BMR

R. Altschul and A. Hoffer. From the Department of Anatomy, University of Saskatchewan, Saskatoon, Canada.

It seems well established that relatively high doses of nicotinic acid have a distinct influence on serum cholesterol in man and rabbits (Altschul, Hoffer and Stephen; Altschul; Parsons et al.; Hoffer and Callbeck; O'Reilly et al.). The mechanism of this effect, however, is still debatable. In an attempt to clarify some factors involved, 12 healthy young adults (students) were given 1 Gm. nicotinic acid 3 times daily for a period of 2 weeks. Before and during the treatment, immediately after cessation, and 1 week later, the BMR and the serum cholesterol levels were determined. The BMR rose only slightly although significantly, whereas the serum cholesterol decreased markedly. There was no parallelism between increase in BMR and decrease in serum cholesterol. It also appeared, as found by Hoffer and Callbeck in a larger series, that in humans with low initial cholesterol level high doses of nicotinic acid are followed by a rise of this level. Finally, a seemingly very important finding that has not previously been taken into account, is that to get comparable results the dosage of nicotinic acid has to be carefully adjusted to body weight.

2:10

53. Success of Niacin and Failure of Niacinamide in Reducing Plasma Cholesterol Levels in Patients with Hypercholesterolemia

William B. Parsons, Jr. and John H. Flinn. From the Jackson Clinic and Jackson Foundation, Madison, Wis.

Large oral doses of niacin (3 to 6 Gm. daily) were administered to 24 patients with hypercholesterolemia. For the first 12 weeks, a daily dose of 3 Gm. was used. If the plasma cholesterol level was higher than 250 mg./100 ml. after 12 weeks, the daily dose was increased to 4.5 Gm. and later to 6 Gm./day in some cases, depending on the response. After 30 weeks, niacinamide was substituted in dosage equal to the most effective dose of niacin. Patients continued to eat their customary diets.

Eight patients (group 1) have been followed for 34 to 42 weeks and 16 additional patients (group 2) for 12 to 32 weeks. The mean plasma cholesterol level for all 24 patients fell from 325 mg./100 ml. before treatment to 269 mg. per cent after 2 weeks and to 263 mg. per cent at the end of 12 weeks of niacin therapy.

Significant reduction in plasma cholesterol levels has thus far been observed in 16 of 24 patients (66.7 per cent) followed for 12 to 42 weeks including 7 of 8 patients (87.5 per cent) followed for at least 30 weeks (group 1). Seven of the 8 patients who have not shown significant reduction have not yet received doses of 6 Gm. daily, inasmuch as they have been treated for shorter periods (group 2).

Of the 8 patients of group 1, 6 had normal plasma cholesterol levels (less than 250 mg. per cent) after 30 weeks, and the level in 1 of the remaining 2 patients had been significantly reduced (480 to 262 mg. per cent) but not to normal. Group 1 showed a mean plasma cholesterol level of 334 mg. per cent before treatment, 270 mg. per cent after 2 weeks, 266 mg. per cent after 12 weeks, and 252 mg. per cent after 30 weeks of niacin therapy.

Doses of 4.5 or of 6 Gm. of niacin/day were required in more than 50 per cent of patients. Of 5 patients who received 6 Gm. daily, plasma cholesterol levels reached normal in all but 1 and were consistently normal in 3. Based on these results, similar improvement is anticipated in 7 of other patients who have failed to respond to 4.5 Gm. daily and who will now receive larger doses.

Substitution of niacinamide resulted in prompt return of plasma cholesterol to pretreatment levels in every instance.

The absence of significant side effects or toxic effects previously reported by Parsons et al. (Proc. Staff Meet., Mayo Clin. **31:** 377, 1956) was confirmed.

The results suggest that the use of large doses of niacin may prove to be the most practical method introduced to date for reduction of elevated plasma cholesterol levels to normal without dietary restriction. The failure of niacinamide opens a new avenue of investigation regarding the mechanism which regulates levels of blood cholesterol.

2:20

54. Treatment of Hypercholesteremia with Nicotinic Acid

Richard W. P. Achor, Kenneth G. Berge, Nelson W. Barker and Bernard F. McKenzie. From the Sections of Medicine and Biochemistry, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Nicotinic acid has been administered orally to 45 patients with hypercholesteremia in doses varying from 1.5 to 6.0 Gm./day for periods of up to 2 years. All other therapy, including diet, was continued unchanged during the study. This method of treatment achieved significant and sustained reductions in the concentration of cholesterol and total lipids

in the plasma and of serum β-lipoprotein cholesterol in a majority of patients. A direct dose-effect relationship was demonstrated when the amount of drug was increased or decreased. As a group, women had a better result than did men, whereas the response of those individuals with xanthoma tuberosum was less than the average for the entire group. Following substitution of a placebo for the nicotinic acid, there was prompt return of the concentration of lipids to pretreatment values. The magnitude of response to nicotinic acid therapy varied widely with different patients, but was reasonably reproducible for each individual.

Side effects consisted chiefly of cutaneous flushing and pruritus, which were severe initially but subsided promptly and were well tolerated. Anorexia and nausea were occasionally troublesome and caused treatment to be stopped in 3 patients. Although physical and laboratory examinations disclosed no untoward effects of therapy with nicotinic acid, 1 man sustained an acute myocardial infarction during treatment, made an uneventful recovery, and has been continued in the study. Two patients died suddenly from coronary heart disease during the period of placebo administration.

Subjective improvements were noted by most patients, but these could not be correlated with any objective findings. The use of nicotinic acid in large doses to reduce increased concentrations of blood lipids appears effective, practical, and probably free from serious harmful effects.

2:30 Discussion

2:45

55. Effect of Dietary Protein on the Serum and Total Cholesterol and the Carcass Fat Composition of Growing Chicks

N. T. Rand, S. N. Shah, C. J. Argoudelis and F. A. Kummerow. From the Department of Food Technology of the University of Illinois, Urabna, Ill.

Sixty-six different groups of day-old chicks in 7 separate series were kept in 3 replicates of 10 birds each on diets varying in the concentration of protein, fat, crude fiber and energy. The experiments were terminated after 4 weeks and the 2 chicks nearest to the average weight in each replicate, e.g., 6 birds for each group, were subjected to total protein and fat analyses.

The results indicated that dietary fat improved weight gain, nutrient utilization and protein retention. The best performance was obtained when fat contributed between 20 and 38 per cent of the total metabolizable energy. However, the beneficial effect of dietary fat on both weight gain and protein retention was pronounced at even the highest fat level. At this point fat contributed up to 97 per cent of the nonprotein calories, indicating that the tolerance for fat per se is essentially unlimited provided adequate amounts of dietary protein are fed.

The percentage of fat in the carcass was increased with decreased protein consumption. For example, twice as much total carcass fat was found in birds kept on a 15 per cent as compared with 30 per cent protein at the same dietary fat level. The amount of fat in the carcass was inversely correlated with the protein/energy ratio and with the ratio of protein intake to relative growth rate. The total fat content of the carcass was not affected by the dietary fat level.

An analysis of the mixed fatty acid composition of the total fat indicated that dietary protein influences the ratio of saturated vs unsaturated fatty acids deposited in the tissue. Furthermore, the amount of total body cholesterol was also influenced by the level of dietary protein and as has been shown previously, the level of serum cholesterol.

2:55 Discussion

3:00

56. Fibrinous-Type of Atheroma in Rats

George F. Wilgram. From the Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada

Recent experiments in several laboratories have shown that atheroma-like lesions may be induced in the coronary arteries of rats. Work in our laboratory has demonstrated that calcified atheromas and coronary occlusion may be induced in this species, although for many decades it has been believed resistant to the induction of experimental atherosclerosis. These changes are producible by a combination of hyperlipemia and vascular injury. These atherosclerotic lesions in rats do not resemble human atherosclerosis fully, but they may be considered as the morphologic equivalent to their human counterpart in terms of the anatomy and histology of the rat. Stainable lipid is very conspicuous in these lesions. Occasionally, however, we encounter lesions where the lipid component is less pronounced. Instead, a fibrin-like material strikingly appears. This fibrin-like material is deposited onto the intima and is being covered with overgrowing endothelial cells. The underlying media is slightly edematous and shows occasional signs of increased cellularity in certain areas. These fibrinous lesions probably occur spontaneously in old rats. We will contrast these fibrinous spontaneous lesions with the experimental changes that are rich in lipid. Although both types of lesions may be termed as "atheromatous," we propose that the fibrinous and the fatty changes respectively have a different etiology. This finding would tie in well with the concept that atherosclerosis is a multifaceted or a polyetiologic disease.

3:10 Discussion

3:15

57. Lipfanogen and Antilipfanogen Levels in Diabetes before and after Insulin

Charles R. Harmison and Henry S. Simms. From the Department of Pathology, Columbia University College of Physicians and Surgeons, New York, N. Y.

Because of the high incidence of atherosclerosis in diabetics, a study of lipfanogen and antilipfanogen levels of diabetics in acidosis and during recovery was undertaken. Initial blood samples from patients in acidosis were drawn before insulin therapy, and second samples were taken 6 to 24 hours later. The levels of the free lipfanogens and of free antilipfanogen were determined by tissue culture methods. Cholesterol determinations were done in most cases.

Free lipfanogens were elevated in diabetic acidosis, but after insulin they fell in 18 out of 20 cases, with a mean decrease of about 30 per cent ($p < 0.001$). At the same time the free antilipfanogen (which was low before treatment) rose after insulin in 17 out of 20 cases, with a mean increase of 130 per cent above the initial level ($p < 0.001$).

In 83 per cent of the cases where cholesterol was determined there was a parallel decrease in free lipfanogens and total cholesterol. In 75 per cent of the cases there was a simultaneous rise in free antilipfanogen and fall in total cholesterol. These findings are consistent with our previous studies.

3:25 Discussion

3:30

58. Inhibition of Cerebrovascular Lipid Infiltrations by Estrogen Administration in the Chick

T. Kuroyanagi, S. Rodbard and C. Williams. From the University of Buffalo, Chronic Disease Research Institute, Buffalo, N. Y.

While considerable attention has been given to the effects of hypercholesteremia on the aorta and coronary vessels, limited work has been done on cerebral and other arteries. In the present study we have given particular attention to the effects of cholesterol feeding on the tendency to lipid infiltration of the cerebral arteries, and have examined the effect of estrogen administration on these and other vessels. Chicks receiving a normal mash diet showed no arterial fatty infiltrations or atheroma. When the diet was supplemented for 5 weeks with 2 per cent cholesterol and 5 per cent cottonseed oil, hypercholesteremia resulted and lipid infiltrations were observed grossly as well as microscopically in the arteries of the brain, heart, kidney and spleen, and in the aorta. Administration of estrogen to chicks on this cholesterized diet resulted in a somewhat higher cholesteremia and a more marked lipid infiltration of the aorta as well as of the kidney and spleen. However, the intima of the coronary arteries was relatively free from fatty infiltrations and atheromatosis. The intracerebral arteries showed similar marked reductions in lipid infiltration and atheromatosis. These results indicate that estrogen has a selective protective action on the arteries of heart and brain, while blood vessels of other organs remain unprotected. It is of interest that the cholesterol plus phospholipid content of brain and heart are much higher than other organ systems. These data may bear on the fact that coronary and cerebral arterial diseases are often concurrent.

3:40

59. Effect of Exercise and Androgen on Cholesterol-Fed Capons

Harry Y. C. Wong, Frank B. Johnson, Abbie Wong, Joseph Anderson and David Liu. From the Department of Physiology, Howard University College of Medicine and Department of Histochemistry, Armed Forces Institute of Pathology, Washington, D. C.

Earlier studies in our laboratory revealed that exercise and testosterone propionate in cholesterol-fed cockerels resulted in a marked reduction of the blood cholesterol and a subsequent reduction in the formation of aortic atherosclerosis of young cockerels (Fed. Proc. **15:** 659, 1956 and **16:** 138, 1957). The present investigation was undertaken to study the effects of exercise and testosterone propionate in cholesterol-fed capons, and to determine whether caponization of cockerels would protect them against atherosclerosis when placed on a high cholesterol diet. Six groups of capons were used in the study: (1) controls on plain mash without therapy; (2) controls on plain mash but exercised; (3) cholesterol-fed only; (4) similarly treated as group 3 with the exception these were exercised; (5) cholesterol-fed capons treated with testosterone propionate only; and (6) similarly treated as group 5 with the exception these birds were exercised twice daily for 30 minutes. The "atherogenic" diet consisted of 2 per cent and 5 per cent cottonseed oil mixed with mash. At the end of 11 weeks of treatment, the following results were observed: (1) cholesterol-fed capons not exercised had the highest incidence of aortic atherosclerosis and blood cholesterol, and (2) birds treated with testosterone propionate or exercised had a significantly lower blood cholesterol and a marked reduction in severity of aortic atherosclerosis when compared to the controls on plain mash or cholesterol-fed only. Influence of exercise and testosterone propionate on the coronary arteries will also be presented.

3:50

60. Experimental Hormonal Therapy of Atherosclerosis: Preliminary Observation on the Effects of Two Compounds

F. W. Davis, W. R. Scarborough, B. M. Baker, M. L. Singewald and R. E. Mason. From Baltimore, Md.

Preliminary observations of the effects of 2 new compounds in patients with coronary atherosclerosis are reported. In animals both drugs were thought

to have serum lipid activity of estrogenic nature, with less feminization than found with ordinary estrogen. Forty-three patients have been studied and compared with 13 given conventional estrogens. The electrocardiogram, ballistocardiogram, BCG cigarette test, total cholesterol, and paper electrophoretic lipoprotein distribution were observed during control and treatment periods. The premise that the young female pattern of serum lipoprotein distribution is desirable was tentatively accepted and efforts to attain this pattern without undue feminization were made. Such effects were accomplished in 50 per cent of patients treated with 1 of the 2 compounds (Manvene). Other evidences of objective improvement were not definitely established, although some suggestion of electrocardiographic and ballistocardiographic improvement over and above that expected in untreated patients was noted. From these relatively short term observations (3.8 months average, with Manvene) it would seem that the possibility of extended therapy with Manvene, in quantity sufficient to favorably influence serum lipids (and possibly other objective measurements) exists, with prohibitive feminization occurring in far fewer patients than appears during ordinary estrogen treatment.

4:00 Discussion

4:15

61. Life Expectancy in Coronary Atherosclerosis and in the Atherosclerotic American Adult Population

Lester M. Morrison and Theodore L. Clemens. Los Angeles, Calif.

Studies are presented which analyze the mortality rates in 100 cases of proven coronary arteriosclerosis who had coronary thrombosis with myocardial infarction following 10 years of controlled observation. Fifty of these patients who survived their initial attack of myocardial infarction were placed on a low fat (25 mg.) diet and 50 other surviving patients were observed who had no dietary restrictions. A sharp reduction in mortality rate from recurrent coronary thrombosis in the dietetically treated group of patients is presented and analyzed as compared with the control group of patients without dietary restrictions.

The author's series of these dietetically-treated patients is assembled and compared together with published series of cases similarly treated. Comparative studies and slides are presented on the mortality rates and dietary factors in general populations from atherosclerotic, cardiac and cerebrovascular diseases, in the United States, Scandinavian and other countries.

A series of tables show new insurance company statistics on increased life expectancy through weight reduction in overweight individuals. The dietary aspects of this increase in life expectancy are dismissed. From these tables it is now possible to check the age of any overweight person and determine his expected age of death. Comparative tables take the same individual and, based on biostatistical evidence, make it possible to estimate the new expected age of death if the individual reduces his weight to the normal or ideal weight. The addition of a given number of years to each individual's life is thus estimated in both sexes from age 25 to 60.

4:25 Discussion

TO BE READ BY TITLE

62. Lipoprotein Patterns of Dogs Maintained on Low and High Fat Diets

Liese L. Abell and Forrest E. Kendall. From the Columbia University Research Service, Goldwater Memorial Hospital, and the Departments of Biochemistry and Medicine, Columbia University, New York, N. Y.

Long-term comparative studies were made of the serum lipid and lipoprotein pattern of dogs maintained first on a diet supplying less than 5 per cent of the calories as fat and then on diets supplying 40 per cent of the calories as fat (lard or corn oil). Serum samples were analyzed during both periods for total lipids, cholesterol, and phospholipid, and were fractionated in the preparative ultracentrifuge into lipoprotein fractions having specific gravities (I) less than 1.063, (II) between 1.063 and 1.11, and (III) between 1.11 and 1.22. Electrophoretically, fraction I is predominantly β-lipoprotein, whereas fractions II and III are α-lipoproteins. The shift from a low fat to a high fat (lard) diet resulted in a consistent slight increase in the serum cholesterol levels. The substitution of corn oil for lard produced no further change in the cholesterol levels of the female dogs, but was associated with a drop to control levels in the male dogs. In dogs receiving thiouracil (50 mg./Kg.), a shift from the low fat diet to the high fat diet (lard) resulted in an increase of 100 mg. per cent in the serum cholesterol level.

The level and composition of the lipid moiety of the 2 α-lipoprotein fractions were constant and did not change as the total serum cholesterol increased in response to cholesterol feeding or thiouracil administration. All of these changes in the serum lipids were due to changes in the level and composition of the β-lipoprotein fraction. However, serum from dogs on a cholesterol-thiouracil regimen showed a significant drop in the α-lipoprotein fraction as well as a large increase in the β fraction. In these animals the total amount of α-lipoprotein had fallen to within the levels seen in human sera.

63. Metabolic Effects of Thyroxine Analogs on the Cholesterol Fed Rat

Maurice M. Best and Charles H. Duncan. From the University of Louisville School of Medicine, Louisville, Ky.

We have previously presented data indicating that the formic acid analog of thyroxine, tetraiodothyroformic acid (TFA-4) differs qualitatively from thyroxine (T-4) in its physiological effects, having a disproportionately greater effect on cholesterol metabolism than in thiouracil-induced goiter prevention. Triiodothyronine (T-3) and its formic acid analog triiodothyroformic acid (TFA-3) have now been studied.

In a control group of 300 Gm. male albino rats, the addition of 1 per cent cholesterol and 0.5 per cent thiouracil to their diet for 2 weeks resulted in a mean increase in thyroid weight from 6.5 to 18.9 mg./100 Gm. body weight. The minimum daily dose per 100 Gm. body weight of each of the four compounds which prevented thyroid enlargement was as follows: T-3, 0.8 μg.; T-4, 3 μg.; TFA-3, 900 μg.; and TFA-4, 3500 μg.

The mean liver cholesterol in the control animals was 1162 mg./100 Gm. liver. Daily administration of 1750 μg./100 Gm. TFA-4, one-half the goiter preventing dose, resulted in mean liver cholesterol of 313. In groups of rats receiving each of the other 3 compounds in approximately full goiter preventing dose the mean liver cholesterol levels were as follows: T-4, 744; T-3, 663; TFA-3, 615 mg./100 Gm. liver.

Oxygen consumption was determined in 4 groups of rats, and expressed as milliliters of oxygen consumed/10 minutes/100 Gm. body weight$^{2/3}$. The addition of 0.5 per cent thiouracil to the diet for 2 weeks resulted in a decrease in oxygen consumption from 29.5 ± 1.4 to 21.7 ± 1.8. The daily administration of TFA-4, 1750 μg./100 Gm., to thiouracil fed rats resulted in oxygen consumption of 26.4 ± 1.4. The administration of T-4, 1.5 μg./100 Gm., resulted in mean oxygen consumption of 25.4 ± 1.8.

It would appear that TFA-4 resembles T-4 in that its effect on oxygen consumption parallels its thiouracil goiter inhibiting activity, but differs in its disproportionately greater effect on cholesterol metabolism.

64. Inhibition of Aortic Atherogenesis in the Parakeet by Stilbestrol

Thomas R. Blohm, Marie E. Winje, Takashi Kariya and Maurice Kane. From the Department of Biochemistry, Research Laboratories of the Wm. S. Merrell Company, Cincinnati, Ohio.

In a previous study (Circulation **14:** 497, 1956) it was found that a high cholesterol diet produces hypercholesteremia and atherosclerosis of the thoracic portion of the aorta in young sexually-mature parakeets. Massive dosage with stilbestrol (about 30 mg./Kg. 3 times a week) produced elevation of plasma phospholipid in control and cholesterol-fed birds, with reduction of the cholesterol/phospholipid ratio in the latter group. Striking inhibition of aortic atherogenesis was also seen: 10 of 14 parakeets fed cholesterol diet only, exhibited atheromata; 1 of 11 birds fed cholesterol and given stilbestrol had lesions.

In the present study, 6 to 8 week old male parakeets were placed on a seed diet containing 1 per cent cholesterol and 5 per cent cottonseed oil, and divided into 3 groups: I, control, subcutaneous oil injections; II, low dose stilbestrol, 0.1 mg./30 Gm. bird, 3 times a week; III, high dose stilbestrol, 1.0 mg./bird, 3 times a week. The birds were sacrificed after 7 weeks,

Group	Plasma total cholesterol (mg. %)	Plasma phospholipid (mg. %)	C/P	Birds with lesions
I	1518 ± 345	771 ± 56	1.76 ± .28	11 of 14
II	1225 ± 345	739 ± 115	1.39 ± .16	6 of 14
III	579 ± 220	440 ± 107	1.10 ± .17	3 of 14

Severity of lesions covered a wide range in all groups.

These birds were sacrificed before onset of puberty. There is a great difference between the response of plasma lipids to stilbestrol in these parakeets and in those in the previous study, which were adolescent. The apparent ability of large doses of stilbestrol to retard the development of hypercholesteremia during sexual immaturity may account for the inhibition of atherogenesis observed in parakeets given this drug. Stilbestrol was well tolerated. Food consumption and body weight were similar in all groups. The high dose of stilbestrol caused a fall in hematocrit, but the low dose did not. No lesions of the coronary arteries or abdominal aorta could be found in any of the birds.

65. Prolonged Low-Dose Estrogen Therapy in Idiopathic Hyperlipemia and Hypercholesteremia

Elaine T. Bossak, Chun-I Wang and David Adlersberg. From the Departments of Medicine and Chemistry, The Mount Sinai Hospital, New York, N. Y.

The effects of long-term treatment with low doses of ethinyl estradiol (Estinyl) on the serum lipids and lipoproteins were studied in patients with inborn errors of lipid metabolism. Only patients who had been on therapy a minimum of 2 months were included in this report.

The group included 4 men and 2 women with idiopathic hyperlipemia, average age 48, and 2 men and 3 women with idiopathic hypercholesteremia, average age 47. Four patients had skin xanthoma

and 2 had xanthoma tendinosa, 5 coronary artery disease and 1 recurrent acute pancreatitis. The average duration of therapy was 8 months (range 2 to 14 months). Doses ranged from .1 to .2 mg. daily. A low-fat diet was instituted prior to the inception of the study and body weight remained stable.

In both groups lipid levels were lower under estrogen therapy. Maximum effects were noted after approximately 6 weeks. In the hyperlipemic group levels of serum total and esterified cholesterol averaged 584 and 393 mg. per cent before therapy and decreased by 50 per cent to 290 and 198 mg. per cent. Total lipids fell 51 per cent from 2909 to 1421 mg. per cent. Average serum phospholipids before and after therapy were 635 and 441 mg. per cent (a fall of 30 per cent). Alpha-lipoprotein increased by 95 per cent from 11.9 to 23.2 per cent of the total stainable lipid. Beta-lipoprotein rose slightly (35.5 to 40.4 per cent) and the O (origin)-fraction decreased from 50.6 to 36.4 per cent.

In the hypercholesteremic group levels of serum total and esterified cholesterol averaged 467 and 358 mg. per cent before therapy and decreased, by 35 and 39 per cent, to 304 and 217 mg. per cent. Total lipids fell 21 per cent from 1321 to 1040 mg. per cent. Average serum phospholipids before and after therapy were 428 and 378 mg. per cent (a fall of 12 per cent). Alpha-lipoprotein increased by 122 per cent from 14.3 to 31.8 per cent of the total stainable lipid. Beta-lipoprotein decreased from 68.9 to 59.2 per cent and the O-fraction decreased from 16.9 to 9.0 per cent.

Levels of lipids and lipoproteins on placebo therapy were unchanged from control levels. Moderate gynecomastia and diminished libido were observed uniformly in men. In 2 postmenopausal women mild uterine bleeding occurred. In 2 patients the cardiac status improved while 3 were unchanged. In 1 patient with extensive xanthoma tuberosa there was gradual disappearance of the lesions during 14 months of estrogen therapy. The present regimen in men and nonhysterectomized women consists of 3 weeks of estrogen therapy and 1 week without medication.

66. High Blood Pressure, Age and Ischemic Arterial Disease

John R. Caldwell. From the Division of Hypertension, Department of Medicine, Henry Ford Hospital, Detroit, Mich.

Sustained blood pressure, fluctuations and known duration of hypertension were related to the age of the patient and clinically significant focal ischemic arterial disease (IAD). One hundred fifty-two patients with hypertension (150/90 or more) had pretreatment basal blood pressures and diagnostic survey. Their average age was 48 years. Twenty-three patients (15 per cent) had IAD and in these the average age was 58 years.

Four groups according to level of basal diastolic pressure were made: (1) <80 mm. Hg—52 patients and 10 per cent had IAD; (2) 81 to 100 mm. Hg—39 patients and 18 per cent had IAD; (3) 101 to 119 mm. Hg—38 patients and 18 per cent had IAD; (4) >119 mm. Hg—23 patients and 15 per cent had IAD.

Lability of blood pressure was indicated as the difference in diastolic between casual office (maximum) and basal (minimum) readings. Less than 16 mm. Hg, slight; 16 to 32 mm. Hg, moderate; and > 32 mm. Hg, marked. In those patients with IAD marked lability was evident in older individuals with low basal pressures. Slight lability was present in younger individuals with high basal pressures.

Known duration of blood pressure elevation was less than 10 years for all 23 cases with IAD. The groups with higher than normal basal diastolic pressures had a similar percentage of cases with IAD present at earlier ages than those with lower blood pressure. Ten per cent of the group with labile blood pressure and normal (<80) basal diastolic pressures had IAD but the average age of this 10 per cent was 70 years.

The incidence of IAD was not greatly different in the 4 groups studied. By comparison, however, signs of hypertensive disease showed striking direct relationship to the levels of basal diastolic pressures.

67. Splenic and Renal "Foam Cell Reaction" Elicited by Manuronate in Lipemic Rabbits

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Previous work in this laboratory showed that injections of Manuronate, started in cholesterol-fed rabbits some time after the establishment of severe lipemia and carried on in the presence of a continued high cholesterol intake, wiped out the lipemia, reduced the hypercholesteremia and arrested the progress of atherosclerosis. Simultaneously, this compound greatly increased the accumulation of lipid-laden foam cells in the spleen and it caused the appearance of lipophages in renal glomeruli ("foam cell reaction"). Given in the absence of a lipemia, Manuronate produced no foam cells. In view of the clinical dangers of an exaggerated foam cell response, a search was made for the principal factors controlling this phenomenon.

In a series of suitably controlled experiments, Manuronate was given for several weeks to groups of cholesterol-fed rabbits with a pre-established lipemia, in the presence of a continued high cholesterol intake. The degree of the ensuing splenic and renal foam cell reaction was assessed by histologic studies, tissue cholesterol determinations, and organ weigh

records. Serial serum turbidity and serum cholesterol determinations were made in each experiment. It was found that, when other factors were kept constant, the foam cell reaction was proportional to the level of pre-established lipemia, the dosage of Manuronate, and the lipid intake during Manuronate treatment. Given at 2.5 mg./Kg., daily, s.c., to animals with an initial serum cholesterol of 300 to 700 mg. per cent, Manuronate exerted a marked and sustained antilipemic effect, without eliciting any foam cell reaction. The marked foam cell accumulation which was produced with 10 mg./Kg. Manuronate and 1700 to 2300 mg. per cent initial serum cholesterol proved completely reversible following discontinuation of both the drug and cholesterol feeding.

68. Effect of Degree of Unsaturation of Vegetable Lipid upon the Plasma and Hepatic Cholesterol Content in the Rat

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Lipids with different degrees of unsaturation, as measured by iodine number, were obtained by use of unhydrogenated oil, completely hydrogenated oil, and a 1 to 1 mixture of the 2. By this method iodine numbers of 130, 1.5 and 61 for corn oil and 137, 1.5 and 57 for safflower oil were obtained. These lipids were incorporated at a 5 per cent level by weight into purified diets. Diets with (2 per cent) or without cholesterol were fed ad lib. to groups of 10 male weanling rats for a period of 8 weeks. No marked differences in rate of weight gain were noted. Scaliness of the rear paw was used as an index of essential fatty acid deficiency, and was found to be most severe in those groups receiving completely hydrogenated oil with cholesterol.

In the absence of dietary cholesterol the degree of unsaturation of the lipid affected neither total plasma or hepatic cholesterol, nor its partition. Similarly, in the presence of dietary cholesterol, plasma cholesterol content was not influenced by the degree of unsaturation. Total hepatic cholesterol increased with the degree of unsaturation in groups receiving cholesterol. The ratio free/esterified cholesterol in the liver decreased with the degree of unsaturation.

69. Effect of Epinephrine on Biosynthesis of Aortic Lipids from Acetate-1-C^{14} in Rabbits

Abraham Dury, Nicholas T. Werthessen and Melvin Nyman. From the Dorn Laboratory for Medical Research, Bradford Hospital, Bradford, Pa., and the Southwest Foundation for Research and Education, San Antonio, Tex.

Recently, we reported significant changes in plasma lipid distribution and transport, and phospholipid metabolism (using P^{32}) of plasma, liver and aorta of rabbits for a few days after a single administration of a dose of epinephrine. In this paper we report further studies on the influence of epinephrine upon aortic lipid-synthetic activity using acetate-C^{14}. Rabbits received epinephrine in oil (0.75 mg./Kg. s.c.) and groups were killed 6, 24 and 48 hours later. Three hours before sacrifice each animal received 1 mc. i.v. of acetate-C^{14}. Controls were injected with peanut oil and then the radioactive compound. Lipid distribution of plasma and liver, plasma glucose and liver glycogen were determined by standard procedures. Aorta lipids were extracted by Delsal's procedure, and measurements done of the amount of radioactivity incorporated in aortic total lipids and 4 chromatographically separated peaks. Although the precise lipid constitution of each peak is not known, we do know that: peak I contains esterified cholesterol, peak II free cholesterol, and peaks III and IV contain phospholipid. Only 24 hours after epinephrine were significant differences found in the amount of C^{14} incorporated into aortic lipid. The amount of radioactivity incorporated into aortic total lipid was 40 per cent of controls, while the amount of radioactivity in peak I was 15 per cent of control value and that of peak IV was significantly decreased ($p = .05$). The percentage distribution of total column radioactivity among the 4 chromatographically separated peaks also was different in the 24 hours group from controls. Peaks II, III and IV had significantly greater percentages of total column activity than found in respective peaks of controls while that of peak I was less than controls. It is noted that previous studies with P^{32} indicated accelerated synthesis of aortic phospholipid at 6 and 12 hours after epinephrine while the data presented here indicate decreased incorporation of C^{14} into aortic lipids at 24 hours but not 6 and 48 hours after administration of epinephrine. Nevertheless, these data are further evidence of the influence this hormone exerts upon aortic lipid metabolism.

70. Steroid Interactions and Estrogen Therapy for Atherosclerosis

Richard A. Edgren and David W. Calhoun. From the Division of Biological Research, G. D. Searle and Company, Chicago, Ill.

A high incidence of feminization complicates the use of estrogenic agents in atherosclerosis therapy. It has occurred to a number of workers that the simultaneous administration of estrogen-antagonists, particularly testoids, may obviate this difficulty; experimental studies have produced encouraging, if not spectacular, results. Our studies of putative steroid antagonists of estrogen activities suggested a

need to reexamine basic assumptions in the laboratory, and perhaps in the clinic. Two lines of evidence bear upon the problem:

1. Though many workers have doubted its validity, the assumption that a particular ratio of antagonist to estrogen will produce a particular level of response has been accepted by default. Yet there are theoretical and experimental grounds for believing that this can not be accepted (see also Villie and Hagerman: Endocrinol. **60:** 552, 1957). The antagonism of estrone-induced uterine growth of mice by certain steroid antagonists resembles to a striking degree a simple molecular competition. In agreement with competition theory but contrary to the "fixed-ratio" doctrine, varying absolute quantities of a single solution containing a fixed estrone-antagonist proportion produced widely differing biological responses. Studies on vaginal smear leucocyte changes of spayed rats suggested similar relationships. 2. Direct evidence of a separation of responses to combination therapy, i.e., qualitatively different responses to the same combination by different tissues, was obtained from vaginal smear studies on spayed rats. Estrone-induced epithelial keratinization proceeded in a relatively normal manner despite testoid doses that had a strong blocking effect upon leucocyte changes. We have elsewhere suggested (Am. J. Physiol. In press) that interacting estrogens may have opposite effects on vagina and uterus.

Although certain testoid to estrogen ratios are known to negate the lipid effects of estrogens (Russ et al.: Am. J. Med. **19:** 4, 1955), we believe that a desired separation of effects may be feasible if estrogen and antagonist are titrated separately.

71. In Vitro Studies of Human Plasma Lipolytic Activity before and after Oral Fat Intake

Hyman Engelberg. Beverly Hills, Calif.

The rate of in vitro lipolysis of added human low-density lipoproteins was determined in 22 normal individuals using fasting and lipemic plasma. Unesterified fatty acid release was found in 16 subjects in all, in 10 in the fasting plasma and in 14 in the postlipemic plasma. The lipolytic activity was greater in the lipemic sample in 8 of the 16 individuals, in 3 it was unchanged before or after fat intake, and in 5 it was higher in the fasting sample. The addition of deoxycholate, which decreases heparin clearing factor and increases pancreatic lipase activity, inhibited lipolysis in most of the subjects, and increased it in a few. Studies using β-naphthol laurate, which in the presence of taurocholate is an excellent substrate for human pancreatic lipase, but not for post-heparin lipolytic activity, showed no hydrolysis in 8 subjects in 6 of whom lipolysis of the lipoproteins occurred. The results of the study suggest that increased plasma lipolytic activity is sometimes present after the ingestion of fat. They further indicate that endogenous heparin lipoprotein lipase is the major plasma enzyme involved in the splitting of neutral fat, but that a lipase similar to pancreatic lipase may be present less frequently in small amounts, and may require added bile for activity.

72. Studies of Human Endogenous Plasma Lipemia Clearing and Lipolytic Activity after Tricalcium Phosphate Adsorption

Hyman Engelberg. Beverly Hills, Calif.

It has been reported that heparin and postheparin clearing factor are adsorbed on tricalcium phosphate gel. The present study has verified this and also shown that human pancreatic lipase activity is not removed by the gel. Studies using tricalcium phosphate gel were done in 14 individuals who had endogenous plasma lipemia clearing activity. The activity was completely or nearly completely removed after gel adsorption, thus affording further evidence of the similarity of the endogenous and postheparin factors. Plasma cholesterol esterase was also apparently decreased in the postadsorptive sample.

73. Effect of Large Doses of Pyridoxine on Serum Cholesterol in the Human

Robert B. Failey, Jr. From the Department of Medicine, Indiana University School of Medicine, Indianapolis, Ind.

Pyridoxine has been shown to be a necessary agent in the conversion of tryptophane to niacin, and the latter substance in its acid form is effective in reducing the serum cholesterol level in the human. To study possible effects of pyridoxine in this regard large doses of the drug were fed to hospitalized patients. Serum cholesterol levels were determined by the method of Zak.

Ten hospitalized males aged 53 to 80 were fed 400 mg. of pyridoxine hydrochloride daily. These patients were in a good nutritional state and were chronically ill with pulmonary fibrosis and/or cardiac insufficiency. Control levels of serum cholesterol, determined daily over a 4 day period, averaged 222 mg. per cent. On the following 10 days patients received pyridoxine hydrochloride 100 mg. q.i.d. During this period serum cholesterol, determined on 5 separate days, averaged 226 mg. per cent. The drug was then stopped, and 5 daily determinations on 8 of the following days averaged 229 mg. per cent. No effect of any significance was observed at this time.

Six hospitalized males of the group above were studied separately over a longer period of time. Four control levels, determined over a 10 day period,

averaged 261 mg. per cent. Pyridoxine 200 mg. q.d. was fed over a 19 day period, and 4 cholesterol determinations during this period averaged 241 mg. per cent. The drug was then increased to 400 mg. q.d., and 4 cholesterol determinations during this period averaged 234 mg. per cent. Four determinations during an 18 day control period immediately following averaged 242 mg. per cent. Results of this phase of the experiment appear to show a fall in serum cholesterol which is significant at the 5 per cent level.

Five hospitalized female diabetics under good control but with minor degrees of arteriosclerosis obliterans showed control serum cholesterol levels averaging 253 mg. per cent. On treatment with pyridoxine 400 mg. q.d. serum cholesterol averaged 234 mg. per cent. Periods of observation here were variable.

These results do not point to any marked clinical usefulness when pyridoxine alone is used at this dosage level. The longer term experiment, and the results with diabetics suggest that the drug does have an effect in lowering serum cholesterol. In view of the effect of pyridoxine as a rather general stimulant of many forms of metabolic activity, it seems possible that this drug may be useful in conjunction with nicotinic acid or other agents in lowering serum cholesterol in the human.

74. Total Cholesterol and Protein-bound Radioactive Iodide in the Tissues of the Adrenalectomized Rat

William C. Foster. From the Department of Physiology, Hahnemann Medical College, Philadelphia, Pa.

A study was made of the total cholesterol content and the protein-bound radioactive iodide in the tissues of 3 groups of adrenalectomized, adult, Wistar-strain rats. Determinations were made on heart and skeletal muscle, liver, kidney, spleen, salivary glands, stomach and duodenum. After adrenalectomy rats were maintained on a diet of laboratory chow and 0.9 per cent sodium chloride solution for 1, 7 and 11 weeks. Before sacrificing, the rats were injected with either 5 or 10 μc. of carrier-free radioactive sodium iodide per 100 Gm. body weight and 4-hour uptake studies made. After sacrificing the tissues were quickly excised and weighed for both total cholesterol and tissue protein-bound radioactive iodide determinations. For the cholesterol studies micro quantities of tissues were homogenized in a tissue grinder and treated by a modification of the method of Schoenheimer and Sperry. For the protein-bound radioactive iodide studies the tissues were suspended overnight in cold trichloracetic acid, washed in excess distilled water and the radioactivity determined. Heart muscle cholesterol decreased slightly.

75. Correlations Between High Density $-S_{1.21}$ 0–20 (alpha) Serum Lipoprotein Level, Serum Lipid Phosphorus Concentration and the Degree of Esterification of Serum Cholesterol

Robert H. Furman. From the Cardiovascular Section of the Oklahoma Medical Research Foundation and the Department of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

Previous studies from this laboratory (J. Clin. Invest. **36:** 713, 1957) in subjects with altered serum lipids accompanying obstructive jaundice revealed significant positive correlations between high density $-S_{1.21}$ 0–20 (alpha) lipoprotein concentrations and the esterified cholesterol concentrations, and between the per cent esterification of cholesterol and the log of the ratio $\frac{-S_{1.21}\ 0\text{–}20\ \text{lipoprotein}}{\text{unesterified cholesterol}}$.

Similar scrutiny of serum lipid and lipoprotein values was carried out in normocholesterolemic nonjaundiced subjects, in whom marked alterations in high density $-S_{1.21}$ 0–20 and lower density $-S_{1.21}$ 25–40 (beta) lipoprotein concentrations were induced by the administration of androgens or estrogens. High density $-S_{1.21}$ 0–20 lipoprotein concentrations are regularly reduced by androgens, increased by estrogens. Characteristically, lower density $-S_{1.21}$ 25–40 lipoprotein concentrations change in a direction opposite to that of the high density lipoproteins during gonadal steroid administration, and there is therefore usually little or no change in chemically-determined serum total cholesterol levels, in spite of marked changes in α-β lipoprotein ratios.

Twelve females and 11 males, ranging in age from 7½ to 83 years, were given 1 or more courses of a variety of androgens or estrogens. Significant positive correlations were found to exist between (1) the concentration of high density $-S_{1.21}$ 0–20 lipoprotein and lipid phosphorus levels ($z = 0.77$, $S.E._z = .102$), (2) the concentration of high density $-S_{1.21}$ 0–20 lipoprotein and esterified cholesterol levels ($z = 0.37$, $S.E._z = .15$), and (3) between the per cent esterification of serum cholesterol and the log of the ratio of $-S_{1.21}$ 0–20 lipoprotein concentration to unesterified cholesterol concentration ($z = 0.63$, $S.E._z = .15$).

Thus are revealed correlations between lipids determined by chemical means and lipoproteins defined solely by physical means. These correlations have predictive value and metabolic connotations of physiologic significance.

76. Cholesterol Analyses of Sudanophilic Streaks in Human Aortas

Jack C. Geer, William Webster, Melvin A. Nyman and Henry C. McGill, Jr. From the Department of

Pathology, Louisiana State University School of Medicine, New Orleans, and Southwest Foundation for Research and Education, San Antonio, Tex.

Human aortas have been analyzed for cholesterol content after gross sudan IV staining in order to correlate the concentration of cholesterol with intimal sudanophilia. A single aorta taken from a case of accidental death and having only fatty streaks was divided into 189 samples representing the intima and 2 different levels of the subjacent media from each of 63 areas. The cholesterol concentrations of the medial specimens were remarkably constant, but the intimal values were highly variable and were closely correlated with the extent and intensity of sudan staining.

Similar representative samples from the aortas of 7 white and 7 Negro individuals between 11 and 15 years of age were also analyzed. These age and race groups were selected because a fourfold difference in fatty streaks has been demonstrated between the 2 races in these ages. Stained intimal tissues were always higher in cholesterol than the adjacent unstained intima, but there were stained intimal tissues which were lower in concentration than unstained intima from other aortas. Thus, there was no constant concentration of cholesterol above which sudanophilia became apparent.

As for unstained intimal tissue, although there was considerable variation from one aorta to another, the concentration of cholesterol in unstained intima from the Negro cases averaged twice that of the white cases. Cholesterol concentrations of the media were relatively constant from one specimen to another, and also from one race to another, regardless of staining or lack of staining in the overlying intima.

These observations are interpreted as evidence that local factors other than cholesterol concentration must influence the presence of sudan stainable lipid in the aortic intima.

77. Use of Massive Doses of Vitamin E in Humans and Rabbits to Reduce Blood Lipids

I. J. Greenblatt. Messinger Research Laboratories, Beth-El Hospital, Brooklyn, N. Y.

Humans were given pure d-alpha tocopherol acetate orally at a level of about 40 Gm. daily for as long as a period of 1 month. No side reactions, weight gain, or loss, occurred.

Blood serum cholesterol and β-lipoprotein determinations were done on 6 male subjects. Their diets were kept constant and after the control levels were established, they ingested the pure vitamin E in 3 divided doses. Two of the patients had xanthoma tuberosum, another a hypercholesterolemic, and the others were normal controls. Some of the patients were followed for as long as 4 months. The most effective decreases in serum cholesterol were in the hypercholesterolemic patients. Two of them showed a fall of approximately 100 mg. of cholesterol after 1 month on vitamin E, with a rebound when the tocopherol was removed that almost reached pretreatment levels. Ultracentrifugation studies of the S_f values were consistent in some of the patients in that the S_f 0–10 class were most responsive to vitamin E ingestion. The fall in S_f 0–10 measured as high as 100 mg. per cent.

The rabbit experiments consisted of 3 groups of animals: group I was fed a standard rabbit chow, group II received 0.75 per cent cholesterol in the diet in peanut oil plus the chow; and group III, 0.75 per cent cholesterol plus peanut oil plus vitamin E at a level equal to 0.5 Gm. of E of body weight/Kg./day. The stock α-tocopherol–cholesterol–peanut oil–rabbit chow mixture was kept refrigerated, except when filling the food bins of the animals. Groups II and III showed rapid elevations of serum cholesterol over a 2 month period. Group I remained within normal limits. However, there was a distinct lag of many weeks in rise of serum cholesterol of the rabbits receiving vitamin E plus cholesterol, compared with those receiving cholesterol alone.

78. Treatment of Myocardial Infarction with Heparin

George C. Griffith, James V. Dooley, Hyman Engelberg, Richard Anderson and Willard J. Zinn. From USC School of Medicine, Los Angeles, Calif.

Its availability in concentrated aqueous form has made possible the use of heparin throughout the treatment of myocardial infarction. The purpose in conducting this study was threefold: to determine whether the anticoagulant action of heparin is equal to or superior to that of dicumarol in treating patients with complicated myocardial infarction; to determine whether subcutaneous injection of heparin offers a feasible method of treating patients during their stay in wards of a general hospital; and to uncover the mechanisms involved.

The heparin-treated group numbered 92 patients; the Dicumarol-treated group, 72 patients. Women in the study averaged 72 years of age; men, 67 years of age. We had planned originally that patients were to be assigned alternately to heparin and control groups; however, residents were impressed with the efficacy of heparin and were loath to withhold heparin from patients with the more serious complications. Therefore, at the start of treatment, 20 per cent of the heparin-treated group were in shock, as compared with only 8 per cent of the Dicumarol group; 36 per cent of the heparin group suffered from severe arrhythmia—runs of ventricular premature beats, severe heart block, etc.—as compared with 15 per cent of the Dicumarol group;

nd although congestive failure was only slightly more common in the heparin-treated group, many more of the heparin-treated patients suffered from severe congestive failure or pulmonary edema.

Results. Thromboemboli in the heparin-treated group totaled 11 per cent; thromboemboli in the Dicumarol-treated group, 16 per cent. Bleeding was more frequent in the heparin-treated group: 9 instances, as compared with only 2 in the Dicumarol-treated group. However, major hemorrhage occurred in only 2 patients of the heparin-treated group. One instance of major hemorrhage occurred in a Dicumarol-treated patient.

79. Silicic Acid Chromatography for the Study of Complex Lipid Mixtures

J. Hirsch and E. H. Ahrens, Jr. From the Rockefeller Institute for Medical Research, New York, N. Y.

The use of columns of silicic acid for the separation of lipids dates from the work of Trappe almost 20 years ago. Borgström, Mead and Fillerup and others have altered the method so as to make it valuable for lipid analysis. The present report describes further modifications which utilize gradient elution and automatic methods of collection and detection. These enable a complete analysis of complex lipid mixtures from a variety of sources.

A petroleum ether solution of the lipids to be analyzed is applied to an 18 Gm. column of specially prepared silicic acid. Elution is carried out with a gradually increasing concentration of ethyl ether in petroleum ether. This eluant is provided by an automatic mixing device placed above the column. Small fractions, automatically collected, are analyzed for lipid content. Completely automatic methods of lipid analysis are now under investigation.

The application of this method to the analysis of serum lipids enables separations into the following lipid classes: hydrocarbons (carotene), cholesterol esters, triglycerides, nonesterified fatty acids, cholesterol, diglycerides, monoglycerides, cephalins, lecithin and sphingomyelin. Recoveries of lipids applied to the column are quantitative, and separations of all major lipid classes are complete. Mono- and diglycerides are present in appreciable amounts only during heparin-induced clearing of lipemic serum. In lipid mixtures from other sources saturated and unsaturated hydrocarbons can be cleanly separated. The completeness and reproducibility of these separations suggest a multitude of applications in lipid biochemistry.

80. Fat Tolerance Test in Apparently Healthy Young Adults

Kurt Hirschhorn, John F. Heffernan, Jr., Leonard J. Stutman, Richard C. Bozian and Charles F. Wilkinson, Jr. From the Department of Medicine, New York University Post-Graduate Medical School and the Fourth Medical (N.Y.U.) Division, Bellevue Hospital, New York, N. Y.

The fat tolerance test has been described by several authors in the past. With the present renewed interest in this test, it seems proper to determine a normal range among apparently healthy young adults to serve as a working basis. The test is of value in the discovery and diagnosis of familial hyperlipemia, as well as in the study of lipid metabolism in general.

We have studied a number of men and women, aged 20 to 25, who did not have any illnesses as determined by medical history and physical examination. The subjects were also clear of any family history suggesting lipid defects.

Tests with a fat load from 70 to 80 Gm. consisting of normal breakfast foods revealed a mild or minimal rise in neutral fat with clearing in 6 hours or less, the peak being at 3 hours. When unsaturated fats were substituted, the amount of lipemia remained the same, but the peak was postponed to 5 or 6 hours with rapid clearing thereafter.

Preliminary studies were done during these tests to determine any concomitant changes in the clotting mechanism. These studies suggest that shortly following the height of the lipemia there is an increased tendency for clotting. This seems to occur regardless of the type of fat used.

81. Mode of Inheritance in Essential Familial Hypercholesterolemia

Kurt Hirschhorn and Charles F. Wilkinson, Jr. From the Department of Medicine, New York University Post-Graduate Medical School and the Fourth Medical (N.Y.U.) Division, Bellevue Hospital, New York, N. Y.

During the past 20 years, a number of families carrying the trait of essential familial hypercholesterolemia with xanthomatosis have been studied by various investigators as to the method of inheritance.

Almost all of these studies have accepted and confirmed the concept of the inheritance of hypercholesterolemia as an autosomic dominant. There remain, however, 2 schools of thought; those considering it to be a complete dominant, and those calling it an incomplete dominant, with homozygosity a prerequisite for xanthomatosis, increased incidence of coronary heart disease and very high cholesterol values.

We wish to report several new sibships with this defect. Once again, the dominance of hypercholesterolemia is borne out. These sibships seem to show the incomplete mode of dominance in that all very high cholesterol values and xanthomatosis are found only in homozygous individuals.

It is our opinion that these 2 methods of inheritance are not incompatible with each other. We may assume that only 1 gene locus is involved, since the

offspring in all studies show a monozygotic ratio. There exist many examples in experimental genetics of multiple alleles of 1 factor, showing different degrees of dominance, and even occasionally mutating to a recessive form. After analysis of our material, as well as reanalyzing all previously reported families, we strongly believe that such multiple alleles may be responsible for the various types of inheritance reported in essential hypercholesterolemia.

82. Hepatic Cholesterol Levels in Rats Following the Cessation of a High Cholesterol Diet

F. B. Kelly, Jr., C. Bruce Taylor, Stanley Cross, Joanne Wolski and George E. Cox. From the Department of Pathology, Presbyterian-St. Luke's Hospital, Chicago, Ill.

Adult rats received a high cholesterol diet for 2 months. Some were killed while on the cholesterol diet; the remainder were placed on a low cholesterol diet, and killed sequentially. Portions of each liver were extracted in Soxhlet's extractors, and cholesterol determined by the method of Schoenheimer and Sperry. Animals killed while on the diet had hepatic total cholesterol levels of 2000 to 3000 mg. per cent. In the other animals a rapid decline in hepatic cholesterol levels occurred after cessation of cholesterol feeding. Levels fell to normal in 5 days to 3 weeks. The rate of decline varied with age of the animals and type of dietary fat. Calculations indicate that the animals disposed of 100 mg. or more of their hepatic cholesterol during the first 24 hours. Probably the major avenue of disposal is biliary and fecal excretion with shift from liver to carcass playing a lesser role. If a similar rate of excretion existed during cholesterol ingestion, maintenance of high hepatic cholesterol levels would require a total daily absorption considerably greater than the maximum figure of 92 mg. per rat per day reported elsewhere (Lin, Karvinen and Ivy, Proc. Soc. Exp. Biol. & Med. **89:** 422, 1955). The total amount absorbed must be 92 mg. plus the amount excreted daily into the intestinal lumen via the bile and intestinal wall. The data suggest that in any balance study the concentration of cholesterol in body tissues, due to previous ingestion of cholesterol, could significantly affect the apparent absorption of cholesterol.

83. Resonance of Pulsations in Elastic Tubes

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The circulation is a pulsating hydraulic system. It is subject to laws of lineal flow and to laws of pulsating flow. To study the effects of these 2 types of laws, they must be studied separately. To separate the effects of these 2 types of laws, pulsations are produced in tubes of fluid. At their natural frequency the pulsations become resonant or tuned. A lineal flow superimposed upon pulsations produces pulsating flow. Since the flow and the pulsations are independently controlled, the system lends itself to analysis. In resonance, flow and pressure correspond. In dissonance the pressure is excessive in relation to flow. There are 2 kinds of pressure in dissonance; one is an effective pressure which drives the fluid, the other is a useless, ineffective backpressure due to impedance. Impedance, as differentiated from resistance, is one of the characteristics of dissonant flow. In a close-coupled system, impedance is a destructive force. In a pulsating hydraulic system, impedance causes loss of efficiency, excessive pressure, increased impact on the conduit, and strain on the pump. A low-pressure system in dissonance may be subject to greater strain than a high-pressure system in resonance. To correlate pressure-flow relationships, there must be a correction for the presence of impedance. There are indications that the circulation is normally resonant, but in some disorders may become dissonant. Impedance due to dissonance may be a destructive factor in the arterial system. Direct impedance measurements of the circulation are feasible and may be of diagnostic value.

84. Chemical and Pathologic Correlations between Coronary and Aortic Atherosclerosis in Cholesterol-Fed Rabbits

Manuel René Malinow, Amanda A. Pellegrino and Eugenia H. Ramos. From the Pabellón de Cardiología "Luis H. Inchauspe," Hospital Ramos Mejía, Buenos Aires, Argentina.

Fourteen control and 48 male rabbits given 1 Gm. of cholesterol/day, 6 times/week during 3 months, were studied. Upon sacrificing the animals, the following parameters were studied: (a) macroscopic lesions of the aorta; (b) cholesterol content of the aorta; (c) blood cholesterol level, and (d) microscopic coronary lesions. The control rabbits had low cholesterol levels, did not show macroscopic aortic lesions, had very scanty coronary lesions and the cholesterol aortic content was lower than 0.35 Gm./100 Gm. of tissue. The cholesterol-fed animals, although subjected to different experimental procedures, were very similar and are considered together. The blood cholesterol levels varied greatly, ranging from 160 to 1600 mg./100 ml. The cholesterol aortic content showed only a gross correlation with the blood level; a few rabbits maintained a normal aortic concentration in the face of a high cholesterolemia. The degree of coronary involvement also showed a rough correlation with blood levels and a "threshold" was apparently present since no lesions appeared with moderately elevated blood levels (up to 400 mg./100 ml). When the coronary lesions were compared with the aortic cholesterol content, only a

rough correlation was present; although a few rabbits had no coronary involvement with greatly elevated aortic cholesterol content the contrary was also true, namely, a few animals showed coronary atherosclerosis with a practically normal aortic content. The macroscopic aortic lesions were also correlated with the other findings: the aortic cholesterol content increased with an increased severity of the aortic lesions, but a great overlapping between the groups existed and the cholesterol content could be doubled without any lesion appearing; furthermore, lesions grading from 0 to +++ could be found in aortas with similar cholesterol contents. The same rough correlation existed between macroscopic aortic lesions and coronary atherosclerosis or blood levels; thus, some animals had no aortic lesions with high cholesterol levels and vice versa.

The large variability of the correlations between the studied parameters suggests that the coronary and the aortic lesions can vary independently and that, although they are somewhat related with the blood cholesterol level, they depend upon other, still not totally known factors.

85. Effects of Homogeneous Formula Diets on the Clotting Time of Whole Blood

G. A. Mayer, W. Ford Connell and J. M. R. Beveridge. From the Departments of Medicine and Biochemistry, Queen's University, Kingston, Ontario, Canada.

During studies on the effect of various homogeneous formula diets on blood lipids, we investigated the changes of a highly reproducible clotting time test in 42 healthy male medical students. Subjects were studied on various diets for periods of 8 to 16 days. The fat content varied widely in the different experiments. Sufficient amounts were ingested to maintain constant weight. The standard clotting time (S.E. ± 0.13 minutes) was performed every fourth day after an overnight fast.

Results. Slight but significant hypercoagulability developed in subjects on a diet deriving 35 per cent of total calories from butter fat. When a further 25 per cent of calories in the form of corn oil, hydrogenated corn oil or coconut oil was added to the diet containing 35 per cent calories as butter fat, no significant change in the standard clotting time occurred. When the formula deriving 35 per cent of calories from butter fat was modified by the addition of 0.28 Gm. β-sitosterol in 2 Gm. corn oil per 950 calorie portion, no change in standard clotting time occurred. The most marked hypercoagulability developed in subjects on diets containing essentially no fat.

86. Serum Cholesterol Reduction by Lecithin

Lester M. Morrison. Los Angeles, Calif.

A group of 21 hypercholesterolemic patients were treated with lecithin and their serum cholesterol and lipid responses were tested monthly for 3 months. All patients but 2 had previously followed a low (25 Gm.) fat daily dietary intake for periods ranging from 1 to 10 years (average 3 years) but had failed to achieve any further lowering of serum cholesterol or lipid levels. Each refractory case had previously been treated also with various cholesterol-lowering agents without further lowering of serum cholesterol or lipid levels. All patients were given more than the customary amount of lecithin since they had proven resistant to previous diet and cholesterol-lowering agents. Two tablespoonfuls 3 times daily at meals was prescribed or 36 Gm. daily. Their previous low-fat diet was continued. Six of 21 cases discontinued the lecithin because of intolerance to the large quantity taken although smaller amounts of lecithin were well tolerated.

Of the 15 remaining cases studied 12 showed a striking reduction of 41 per cent in serum cholesterol levels. Three cases showed no significant fall in serum cholesterol or lipid intake. These 3 cases failed to respond probably due to the introduction of steroid hormone therapy, increase in dietary fat intake and the induction of gastroenteritis during the lecithin study. Twelve of the 15 cases showed an average of 129 mg. of total serum lipid fall following lecithin administration. A therapeutically desirable relative increase in serum phospholipids with an increase in antiatherogenic ratio of phospholipid to cholesterol occurred in all cases following lecithin therapy. Lecithin was found to be the most effective cholesterol lowering agent tested to date.

87. Changes in Lipid and Lipoprotein Partition Induced by Feeding a Skim Milk-Corn Oil Mixture

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Preliminary studies using 7 individuals hospitalized in an institution providing long term care for ambulatory patients have demonstrated significant alterations in both the cholesterol and lipoprotein partition induced by supplementing the regular diet by feeding skim milk–corn oil mixture. These individuals were maintained on the usual hospital diet but, 3 times daily prior to meals, they were fed 6 ounces of the skim-milk powder–corn oil mixture. This supplement provided 40 per cent of its caloric content from corn oil, the remainder from defatted skim-milk powder. For convenience of administration this material was homogenized in bulk and stored in the frozen state until immediately prior to use.

After several weeks of controlled observation of the spontaneous fluctuations in their lipid and lipoprotein partition, 4 of the 7 individuals demonstrated a 25 per cent–60 per cent decrease in the total cholesterol level after 3 weeks of the supplemental feeding. During this same interval a signifi-

cant fall in total serum lipid was evident. Data on these individuals studied for a longer period of time and on both the quantitative and qualitative changes in serum lipids and lipoproteins will be presented.

88. Electrocardiogram of the Normal Pig in Experimental Coronary Occlusion

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The pig is being used as an experimental animal in cardiac research with increasing frequency because its heart, compared to that of other experimental animals, is claimed to be more nearly similar to the human heart. In 30 normal pigs, the electrocardiogram was studied with limb leads and chest leads taken circumferentially at three horizontal levels.

From the frequency distribution of electrocardiogram patterns in individual leads, normal standards were determined. The distribution range is wide, but compares to that of the human electrocardiogram, in spite of differences of orientation. For analysis of mean spatial QRS, T and P vectors, their null points around the chest circumference and their projections on the frontal and horizontal planes were determined. The orientation of the mean spatial QRS and T vectors is nearly opposite in direction. In the horizontal plane, the average QRS vector points posteriorly, the average T vector points anteriorly. In the frontal plane, the QRS points inferiorly, the T vector superiorly.

In contrast to the human and canine electrocardiogram, the T wave of the normal pig is discordant. The normal pig electrocardiogram, therefore, resembles that of coronary insufficiency in man and most other mammalian hearts. The pig's heart is dissimilar to the human heart electrophysiologically. The reason for the different repolarization pathway is obscure, but may have some bearing on the great vulnerability of the pig's heart to ventricular fibrillation in coronary occlusion. In experimental occlusion of the anterior descending branch of the left coronary artery, the changes of the S-T and T wave were not consistent; in some animals the T wave became concordant instead of discordant and in others the magnitude of the discordant T wave increased.

89. Serum Lipids and Enzymes in Pancreatic Disease

Harold H. Orvis and John M. Evans. From the Department of Medicine, George Washington University School of Medicine, Washington, D. C.

A study of serum lipids and lipid enzymes in 5 patients with pancreatic disease was undertaken to evaluate the role of the pancreas in lipid abnormalities. Two of the patients had acute pancreatitis, 1 patient had pancreatic insufficiency due to chronic pancreatitis and 2 patients had had pancreatectomy for cancer.

Serum total lipid, phospholipid and cholesterol were determined by standard methods. Lipoprotein cholesterol was measured after separation by paper electrophoresis. Lipase was assayed utilizing olive oil and esterase with tributyrin as substrates for hydrolysis. Lipoprotein lipase was evaluated by densitometry employing pooled lipemic sera or an olive oil emulsion as substrates for clearing with postheparin serum and by titration of the hydrolyzed fatty acids.

Four of the patients had low or normal lipid values. The 5th was a patient with acute pancreatitis and hyperlipemia. In this patient total lipid, free and ester cholesterol and phospholipid were markedly increased during the early days of the illness. These values returned to normal as the illness subsided.

The per cent of cholesterol in the β-lipoprotein was observed to be elevated in both patients with acute pancreatitis. In contrast, the remaining 3 patients had low β-cholesterol. Similarly, the serum lipase was elevated in both patients with pancreatitis whereas the value was low in the patient with pancreatic insufficiency and 0 in the patients after pancreatectomy. On the other hand, serum tributyrinase was found to range between 45 and 150 units (normal 80 to 200) in all of the patients, the higher values being obtained in the 2 patients with acute pancreatitis.

The lipoprotein lipase was normal in all but the patient with lipemia. Here, clearing could not be demonstrated by the technics employed, although the presence of this lipase was suggested by the characteristically increased electrophoretic mobility of the lipoproteins. However, this patient eventually showed a normal response to heparin after the illness and lipemia had subsided.

On the basis of these findings it is suggested that: 1. An increase in serum lipase may precede a rise in β-lipoprotein cholesterol and conversely, decreased serum lipase may precede a fall in β-lipoprotein cholesterol. 2. Serum lipase was absent in 2 patients after pancreatectomy. 3. Serum tributyrinase may not be a reliable indicator of acute pancreatic disease. 4. The action of lipoprotein lipase was probably inhibited in the patient with pancreatitis and hyperlipemia.

90. Comparison of Total Cholesterol Levels in Blood Serum with Lipid Concentrations in Human Coronary Arteries: Second Interim Report

J. C. Paterson and J. B. D. Derrick. From the Clinical Investigation Unit of Westminster Hospital, Department of Veterans' Affairs, and the Colloid Medical Research Laboratory, University of Western Ontario, London, Canada.

This report, which is concerned with only 1 facet of our continuing studies on the serum lipid/atherosclerosis problem, gives the results of a comparison of the levels of total serum cholesterol, determined serially during life in 88 patients, with the concentrations of total lipid extracted from large segments of the coronary arteries of the same patients after death and autopsy. No significant relationships have been encountered in individuals between 60 and 89 years of age, whether the comparisons were made on the entire series of cases or on cases in the same age group at the time of death. The data in younger individuals were inadequate for statistical analysis. Terminal loss of weight from wasting disease processes had no significant relationship to the concentration of lipid in the coronary arteries of the entire series of cases or of cases in the same age group. In general, the antemortem serum cholesterol levels of the 88 patients were found to be remarkably constant on serial determination over periods of as long as four years: the mean percentage deviation from the mean of multiple determinations in the entire series was only 10.9. These results in older individuals do not support the contention that "the more fat (cholesterol) there is in the blood, the more fat there is in the arteries."

91. Effects of Various Grain Germs and Grain Oils on Plasma Lipids and Atherogenesis in Cholesterol-Fed Cockerels

Ruth Pick, Jeremiah Stamler and Louis N. Katz. From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

These experiments were designed to test the effects of various grain germs and grain oils on plasma lipids and atherogenesis in cholesterol-fed chicks. The following groups of cockerels were studied during the age period 14 to 19 weeks: (1) control, mash + 1 per cent cholesterol + 10 per cent cottonseed oil; (2) corn, mash + 1 per cent cholesterol + 17.8 per cent corn germ (added fat, 10 per cent); (3) wheat, mash + 1 per cent cholesterol + 17.8 per cent wheat germ + 8.2 per cent wheat germ oil (added fat, 10 per cent); (4) rice, mash + 1 per cent cholesterol + 17.8 per cent rice germ + 7.3 per cent crude rice oil (added fat, 10 per cent).

Hypercholesterolemia and atherogenesis were least in the corn germ group. They were moderately reduced in the wheat germ–wheat germ oil group. They were moderately intensified in the rice germ–rice oil group.

Under these experimental conditions, therefore—with constant fat content in the diet—different grain germs had qualitatively different effects. The mechanisms of these phenomena remain to be elucidated.

92. Arteriopathies as Etiologic Factor of Pancreatic Morbidity

O. J. Pollak. Dover, Del.

Pancreatic diseases have varied etiology. The causative role of arteriopathies seems greater than hitherto believed.

Of 88 adults in whom pancreatic disease was found at necropsy (430 consecutive examinations) 55 had alterations of pancreatic arteries. Extensive calcinosis of the media (arteriosclerosis) of larger pancreatic arteries was found in a patient with extensive pancreatic cirrhosis. The other 54 patients had varying degrees and types of intimal-subintimal lesions (atheromatosis) with yellow plaques (atheroxanthosis), pearly white plaques (atherofibrosis), or calcific plaques (atherocalcinosis).

Seven patients had thrombi in pancreatic arteries. In 5 patients with acute, chronic, or recurrent pancreatitis there were thrombi in larger atheromatous arteries of the pancreas. Two of these patients died of hyperglycemic acidosis. In 2 patients pancreatic artery thrombosis coincided with coronary artery thrombosis: One patient had thrombi in many small arteries leading to miliary necroses of the pancreas; the other patient had thrombi in larger pancreatic arteries and had extremely severe pancreatic steatosis. Fourteen of the 88 patients of the series died of myocardial infarction following thrombosis which had complicated the anatomic disease, atheromatosis.

93. Rabbit as an Experimental Animal for the Study of Coronary Artery Disease

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A positive ergonovine test (depression of the S-T segment of the electrocardiogram) indicates the presence of coronary artery disease in the living cholesterol-fed rabbit (male, Dutch belted). This conclusion is based on the finding that, in 46 rabbits in which a positive ergonovine test was obtained, at postmortem plaques or occlusion of the intramural coronary vessels were seen on microscopic examination. Studies were carried out to determine the effect of diet on the time required for the ergonovine test to become positive. In 18 rabbits fed a 2 per cent cholesterol–6 per cent corn oil diet, positivity occurred in an average of 9.3 weeks; in 14 rabbits on a cholesterol diet without corn oil, it was 23 weeks. However, of 57 animals fed cholesterol and corn oil which lived past 5 weeks, 18 (31 per cent) developed positive tests as compared with 14 of 22 (64 per cent) positive tests in rabbits fed cholesterol alone. The average weight of the former group was 1.93 Kg. at the start of the diet and 1.47 Kg. when the ergonovine test became positive; for the cholesterol without corn oil group, these figures were 1.79 and 2.01 Kg., respectively. A marked hypercholesterolemia may exist in the cholesterol-fed rabbit without any coronary artery disease. On the other hand, the rabbit with advanced coronary atherosclerosis may have little or no elevation in serum

cholesterol. Therefore, the serum total cholesterol in this rabbit cannot be used as an index of coronary atherosclerosis. Likewise, gross changes in the aorta do not parallel coronary atherosclerosis.

The isolated heart of the ergonovine positive rabbit may be successfully perfused to study drug action. The initial state of 29 perfused atherosclerotic hearts was statistically different from that of 32 normal hearts. On the average, prior to drug perfusion, coronary flow was greater, heart rate slower and amplitude of contraction smaller for the atherosclerotic heart. Furthermore, qualitative and quantitative differences in the effect of drugs on the coronary flow for the atherosclerotic and normal hearts were observed. Perfusion of the heart does not preclude subsequent histologic examination of the coronary arteries with hematoxylin-eosin, Weigert's or oil red O stains.

94. Dietary Factors Affecting Unloading of Plasma Cholesterol and Arterial Lipids

S. Rodbard and C. Williams. From the University of Buffalo Chronic Disease Research Institute, Buffalo, N. Y.

Aortic and coronary hypercholesteremia and atheromatosis induced in chicks by dietary means (2 per cent cholesterol) tended to return to normal within a week when a full diet without cholesterol was fed. The presence of cottonseed oil in the diet did not prevent this "unloading" effect. However, unloading was inhibited by adding very small quantities of cholesterol (0.1 per cent) to the diet. When no food was given during the unloading period, the plasma and blood vessel lipids remained high. Dietary elements affecting the unloading processes were studied: feeding of oat hulls, a material without nutritive value, had the same effect as complete inanition; hypercholesteremia and lipid infiltration of arteries persisted with the addition to the oat hulls of (1) a commercial vitamin-mineral mixture, (2) choline and inositol, (3) alcohol or (4) a mixture of amino acids essential for the chick. Sucrose dissolved in the drinking water produced a transitory drop in the plasma cholesterol which then returned to high values; the vascular lesions did not regress. The results show that a normal cholesterol-free diet is required to facilitate rapid unloading of lipids from blood and arteries. These experiments emphasize the deleterious effects of regimens of continuous cholesterol feeding, contrasting with the "beneficial" effects of intermittent periods of relief from ingestion of this material.

95. Clinical Experiences with Safflower Oil: Preliminary Report

Paul B. Roen. Clinic for the Study of Arteriosclerosis, Hollywood Presbyterian Hospital, Los Angeles, Calif.

Unsaturated fatty acids have been shown to have a lowering effect on serum lipids. If unsaturated fatty acids are to offer a useful approach to the management of hypercholesterolemia and atherosclerosis, their practicability must be shown in treating patients of the type seen in clinics and private practice, both with and without clinical evidence of atherosclerotic lesions. Because of its palatability and high iodine number, safflower oil was used in this study.

To date 71 private and clinic patients have received safflower oil over varying periods of time. In many of these cases, pretreatment lipid levels were within "normal" range. The oil has been administered in various ways—in stated amounts, in salad dressing, or in cookery. It has been given with various unrestricted diets and together with a low-lipid diet. In each of the 71 cases, 2 or more lipid determinations have been taken to assess effects of the safflower oil.

Results will be broken down as to sex and age (by decades); type of lesion; stability or instability of serum lipids prior to treatment; cholesterol and phospholipid concentrations; and C/P ratio. A limited number will have A.I., chylomicron counts, and α and β lipoprotein fraction determinations.

96. Effect of Triiodothyronine on Serum Lipids and Lipoproteins of Euthyroid and Hyperthyroid Subjects

Bernard A. Sachs, Ethel Danielson, Marion C. Isaacs and Raymond E. Weston. Medical Division, Montefiore Hospital, N. Y.

The inverse relationship between thyroid production and the level of serum lipids has been well established. The availability of the more potent analog of thyroxine, triiodothyronine, presented an opportunity for studying its effects on the serum lipids and lipoproteins of carefully controlled euthyroid and hyperthyroid subjects maintained on fixed food and fluid intakes on a metabolic ward. l-Triiodothyronine (0.4 to 6.0 mg. daily) was administered intravenously in divided doses for 3 to 23 days to 3 normal subjects, 1 hyperthyroid patient during a partial spontaneous remission, and 1 patient with frank thyrotoxicosis. Hypermetabolism was produced in the euthyroid subjects and increased in the hyperthyroid patients.

Serum total lipids, lipid phosphorus, total cholesterol, β-lipoproteins and protein fractionation (by either densitometry or elution) after paper electrophoresis were determined before, during, and following triiodothyronine administration. Serum lipids and lipoproteins began to decrease proportionally within 1 to 4 days of the onset of therapy. The decrease in total lipid varied from 15 to 50 per cent, in lipid phosphorus from 19 to 56 per cent, and in total cholesterol from 23 to 56 per cent. Profound falls in β-lipoprotein were also observed but changes in protein fractions were inconstant. The serum

lipid partition returned to control values 7 to 15 days after cessation of therapy. The observed fall in lipids persisted after therapy longer than did the other clinical and laboratory evidences of hypermetabolism, which subsided within 4 to 6 days.

Further studies of the lipolytic effects of triiodothyronine are indicated to determine the mechanism of its action and the possible role of lower doses of this potent substance in the treatment of disorders of lipid metabolism.

97. Hormonal Factors in the Hyperlipemia Induced by Protamine

Michael C. Schotz and Irvine H. Page. From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

Protamine is known to induce a hyperlipemia in various animals. This hyperlipemia has been attributed to the inactivation of heparin or heparin-like substances in the enzyme lipoprotein lipase. We have investigated the effect of the adrenals and pituitary on protamine hyperlipemia.

Four groups of rats were used: normal, adrenalectomized, hypophysectomized and adrenalectomized plus cortisone. All animals were starved 16 hours, injected with protamine (1 mg./100 Gm.), killed 60 minutes later, and total serum lipid determined. The normal animals showed an average increase of total lipids of 45 per cent after protamine injection whereas, no significant change was observed in the adrenalectomized or hypophysectomized rats. In the group of adrenalectomized rats receiving small doses of cortisone, protamine injection caused a 40 per cent increase in the total lipids.

These data cast some doubt on the simple explanation that protamine hyperlipemia is due to the inactivation of lipoprotein lipase.

98. Effects of Heparin and Dicumarol on Atherogenesis in Cholesterol-Fed Cockerels

Jeremiah Stamler, Ruth Pick and Louis N. Katz. From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

In view of the growing utilization of heparin and Dicumarol in the long term treatment of human atherosclerotic disease, the effects of these drugs were assessed on experimental atherogenesis in cholesterol-fed cockerels.

Four series of experiments were accomplished using depot heparin (2, 10 and 20 mg./bird/day) in chicks ingesting mash supplemented with 0.5, 1.0 and 2.0 per cent cholesterol plus 5 per cent cottonseed oil. Heparin did not suppress diet-induced hypercholesterolemia, nor did it lower levels of any β-lipoprotein classes in intact, alloxanized or depancreatized cockerels. Coronary and aorta atherogenesis were also unaffected.

In 3 series of experiments with oral Dicumarol (4 to 30 mg./bird/day), a tendency toward aggravation of cholesterol-induced coronary atherosclerosis was observed; no effects were observed on hyperlipemia or aorta atherogenesis. In 2 experiments, heparin partially counteracted the ability of estrogens to prevent coronary lesions, i.e., it apparently exerted a positive atherogenic effect.

Despite prolongation of clotting time, no evidence was obtained of hemorrhage into plaques.

These findings suggest that heparin and Dicumarol—in the presence of the prerequisite dietary and lipid metabolic alteration—may potentiate atherogenesis in the chick.

99. Electrophoretic Studies in Acute and Chronic Coronary Diseases

Joseph Sternberg and Paul David. From the Clinical Research Laboratory, Montreal Institute of Cardiology, Montreal, Canada.

The electrophoretic pattern of the serum proteins, lipoproteins, and glycoproteins has been examined in a group of patients with acute myocardial infarction and with chronic coronary insufficiency. In the patients with acute myocardial infarction, the electrophoretic pattern was examined daily for the first week and every second day for at least another week. In the chronic cases, the examination was performed every 15 days for periods of time ranging from 3 to 6 months; during this period, the patients were under treatment (estrogen or α-tocopherol) or were given a placebo. Simultaneously, electrocardiographic tests as well as other routine cardiologic procedures were carried out in order to correlate the clinical findings to the electrophoretic data.

In acute myocardial infarction (11 cases), the following facts have been found. There is a consistent increase of the α-2 and the α-1-globulins during the first week of the infarction, parallel to the increase of the protein bound polysaccharides in the above fractions. This increase follows closely enough the elevation of the sedimentation rate. Although a rough relationship might be established between the extent of the myocardial damage and the increase in the α-2-globulins, no statistical correlation can be made yet, partly owing to the uncertainty of the polysaccharidic staining. On the other hand, no correlation can be established between the electrophoretic pattern and the electrocardiographic findings. This increase, translating the so-called "stress patterns," can also be found in any other stressant syndrome and is by no means specific to the myocardial infarction; however, the added increase of the β fraction in some cases is more closely related to the acute coronary disease. In two cases, the β fraction was not only increased, but during the first week it was split into two definite fractions; the "split β" was not detectable after the second week of the disease. The lipoproteic pattern was not changed

during the acute period, nor did all the patterns show a large β fraction or a diminution of the α fraction. In the cases showing the split β-proteins, the lipoproteic pattern was identical to that of a normal adult male, suggesting the possibility that the colloidal alteration of the lipoproteins starts in the proteic moiety in these cases.

In the cases of chronic coronary insufficiency (85 clinically proven cases), there was no characteristic proteic or glycoproteic pattern, the extent of the stress probably being insufficient to provoke the increase of the α-globulins or of the protein bound polysaccharides.

The lipoproteic pattern, determined by the use of a special thick paper method, allowed the determination of the neutral fats and of the fatty acids simultaneously with the lipoproteins. No significant change was noted in the first 2 constituents in chronic or in acute coronary diseases.

The β/α-lipoprotein ratio was increased in approximately half of the patients, but it was not possible to find a constant relationship between the 2 phenomena. However, in the patients showing a very high β-lipoprotein, a phenomenon similar to the split β-protein fraction was found to have a predictive value for coronary insufficiency: the β-lipoprotein was split into fractions, the second one being less sharply defined than the first fraction and having a migration speed intermediate to that of the β and of the α fraction, corresponding to the α globulin.

100. Comparison of Early Lesions of Atherosclerosis in New Orleans, Guatemala, and Costa Rica

Jack P. Strong, Carlos Tejada-V., Henry C. Mcgill, Jr. and Russell L. Holman. From the Department of Pathology, Louisiana State University School of Medicine, New Orleans, and Instituto de Nutricion de Centro America y Panama, Guatemala.

In an attempt to account for the great difference known to exist between the incidence of clinical disease due to atherosclerosis in the United States and certain other geographic areas, we have compared the extent of the early lesions of aortic atherosclerosis in 461 aortas collected from the New Orleans area with 227 specimens from Guatemala and 113 from Costa Rica, all from individuals under 40 years of age. Aortas were obtained from large general hospitals and medicolegal pathology services in all three areas. They were stained grossly with sudan IV in order to facilitate detection and quantitation of early lesions. The severity of atherosclerosis was expressed in terms of the percentage of aortic intimal surface covered by each of 3 types of lesions—fatty streaks, fibrous plaques, and complicated lesions.

The degree of involvement of the aortas with fatty streaks was approximately the same at all ages for New Orleans whites, Guatemalans, and Costa Ricans. These 3 groups were all lower than the New Orleans Negro cases at all ages, but most strikingly so between 11 and 15 years of age.

With respect to fibrous plaques, both the Guatemalan and Costa Rican specimens were significantly less severely involved than either the New Orleans white or New Orleans Negro.

Thus there is more difference in the severity of the earliest lesions of atherosclerosis (fatty streaks) between 2 racial groups in the same geographic area than between population groups in widely separated geographic areas. The difference in involvement with fibrous plaques, however, calls attention to the probability that factors which initiate the process of atherogenesis may be quite different from those which influence the progression of lesions to more advanced stages and to clinical disease.

101. Diet, Physical Activity and Serum Cholesterol in Man

Henry Longstreet Taylor, Joseph T. Anderson and Ancel Keys. From the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.

Two experiments were carried out to assess the effects of diet in the presence of physical activity on the serum cholesterol concentration. The general plan was to have a control period (1) of sedentary activity, a period (2) of physical activity requiring an additional 1200 calories of work followed by a second sedentary period (3). In the first experiment 9 male university students were used and in the second, 5. In the first the calories required to pay for the physical activity had the same composition with regard to fat (42 per cent of calories derived from fat) as the diet eaten during the first sedentary period. This increased the total amount of fat eaten by 45 Gm. a day. There was no change in the total serum cholesterol or β-lipoprotein cholesterol in any of the 3 periods. In the second experiment, all calories necessary to pay for work were derived from fat. This increased the per cent of calories derived from fat in the diet from 42 per cent in the first period to 50 per cent in the activity period. In spite of a predicted increase of total serum cholesterol of 28 to 30 mg./100 ml. of serum, no change in the total serum cholesterol concentration was observed in any of the periods. It is concluded that physical activity can modify the effects of diet on the serum cholesterol.

102. Effect of Various Dietary Fats on Blood Lipids of Rabbits

E. Van Handel and D. B. Zilversmit. From the Department of Physiology, University of Tennessee, Memphis, Tenn.

Although it appears well established that certain vegetable oils lower blood cholesterol concentrations of man, there is little information on the effect of these fats on blood lipids of rabbits, a species very susceptible to cholesterol induced atherosclerosis. Most previous work has been performed with diets rich in cholesterol and low in triglycerides. In the present study the effect of fat alone on the blood lipid fractions was investigated. White rabbits were fed 65 per cent purina chow plus 35 per cent of: liquid cottonseed oil or selectively hydrogenated cottonseed oil (linoleate 1.5 per cent) or corn oil. Plasma cholesterol, phospholipid and triglyceride were measured monthly. Even though the animals on this high fat regimen did not grow as much as controls on 100 per cent rabbit chow they maintained an average food intake of 50 Gm./day. Blood triglycerides fluctuated most widely but marked variations also occurred in serum cholesterol and phospholipids. Four months after the beginning of the high fat regimen serum cholesterol or phospholipid concentrations were no higher than at the start even in those animals that exhibited transitory hyperlipemias. In practically all instances the cholesterol-phospholipid ratio stayed constant throughout the experiment and was maintained below unity. No evidence was obtained that isocaloric substitution of hydrogenated vegetable fat for liquid cottonseed or corn oil had any cholesteremic effect. In animals maintained on the high fat diet for 4 months no gross atheromatous lesions in the aorta were noted but the livers appeared uniformly fatty and contained considerable amounts of triglyceride. By the use of P^{32} it was demonstrated that the absence of elevated serum phospholipids was not the result of an inability of the liver to synthesize plasma phospholipids.

103. Studies on Serum Cholesterol Esterifying Enzyme: In Myocardial Infarction, Idiopathic Hyperlipemia and Idiopathi Hypercholesteremia

Chun-I Wang and David Adlersberg. From the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

The activity of the serum cholesterol esterifying enzyme (Sperry enzyme) was studied in 133 persons. A control group included 24 "healthy" men and women without any stigmata of atherosclerosis, especially coronary artery disease The other groups consisted of 31 persons with myocardial infarction and *normal* serum cholesterol levels; 59 with idiopathic hypercholesteremia and 19 with idiopathic hyperlipemia.

Total and free serum cholesterol was determined before and after incubating the serum at 37 C. for 24 hours. The percentage of reduction in free cholesterol after incubation was used as an index for the activity of the cholesterol esterifying enzyme. One per cent reduction was expressed as 1 unit.

In the control group, the activity of serum cholesterol esterase averaged 41 units. In normocholesteremic patients with preceding myocardial infarction the esterase activity averaged 33 units. In persons with idiopathic hypercholesteremia, the activity averaged 28 units; and in those with idiopathic hyperlipemia, 22 units.

The differences between the various groups were statistically significant. The reduction of activity of the esterifying enzyme might be related to the extent of the metabolic error in these conditions.

104. Continued Vigorous Physical Activity as a Possible Factor in the Prevention of Atherosclerosis

Joseph B. Wolffe. Department of Internal Medicine and Cardiovascular Diseases, Wolffe Clinic and Hospital, Philadelphia, Pa., and Valley Forge Heart Hospital and Medical Center, Fairview Village, Pa.

Three hundred athletes actively engaged in vigorous physical activity and 300 top executives, all past middle life, were surveyed for evidence of atherosclerosis.

The following studies were employed to establish part of a profile pattern of atherosclerosis: physical examination, teleradiogram, electrocardiogram, roentgenogram of the abdominal aorta with Bucky technic, blood cholesterol.

Definite or suggestive evidence of atherosclerosis was found in a surprisingly high number among the executive group whose physical activities were curtailed. The athletes actively engaged in vigorous physical activities showed little evidence of atherosclerosis. It was particularly noteworthy that Marathon runners in the fifth and sixth decade showed no evidence of atherosclerosis in the vessels of the lower extremities and good circulatory efficiency was demonstrated. This seems to disprove the often repeated statement that "wear and tear" of life is an important factor in the genesis of this common arteriopathy.

SPECIAL ANNOUNCEMENTS

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

ELEVENTH ANNUAL MEETING

FIRST ANNUAL GEORGE LYMAN DUFF LECTURE:

Sunday, November 3,
Luncheon 12:00 Noon

William Boyd, Former Professor of Pathology in the University of Manitoba, the University of Toronto, and the University of British Columbia

PRELIMINARY REPORT: Committee on Grading of Atherosclerotic Lesions

Sunday, November 3,
11:45 A.M.
R. L. Holman, Chairman

ANNUAL BUSINESS MEETING:

Sunday, November 3,
2:00 P.M.

Presidential Address, Charles F. Wilkinson, Jr., Promethius and Pandora
2:30 P.M.

SMOKER:

Sunday, November 3,
10:00 P.M.

All activities take place in the Grand Ballroom of the Knickerbocker Hotel, Walton Place, Chicago

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